Mysteries of the Mighty Microbiota

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In this issue of the *Biomedical Journal,* we take a close look at the microbial metropolis of the gut and examine its impact on human health. We also highlight an interesting animal study showing that short-term treatment with antioxidants can protect tissues against the genotoxic effects of ionizing radiation. Such reports continue to fuel the hotly debated topic of the benefits of antioxidants. This issue also features several clinical studies examining the efficacy of current treatment regimens for primary breast lymphoma, *Helicobacter pylori*, and multidrug-resistant *Acinetobacter baumannii*. *(Biomed J 2014;37:241-244)*

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SPOTLIGHT ON REVIEWS – The Bacteria that Make you Fat and Other Wonders of the Microbiota

In the stomach, colon, and the dark corridors of the small intestine, our bodies are teeming with microbial inhabitants that outnumber our cells by 10 to 1 [Figure 1]. Collectively termed the "microbiota," recent years have seen renewed interest in these microbial passengers. In this issue of the *Biomedical Journal*, Vijay-Kumar and colleagues discuss many of the aspects of mammalian gut immunity,[1] including the mechanisms underlying immune tolerance toward the gut microbiota, and Lai and colleagues discuss the function of the microbiota and its influence on human health and disease.[2]

The mammalian immune system is faced with the colossal challenge of policing a community of over 100 trillion microbes. Transient pathogens must be detected and eliminated, while beneficial opportunists must be kept on the correct side of the gut epithelial membrane. This formidable task is carried out by the "mucosal immune system" (MIS), which has developed an intricate system of communication with the gut microbiota involving pattern recognition receptors (PRRs) that recognize microbial molecules. The expression of PRRs is tailored to limit their repeated activation, but enables effective responses when threats appear. For example, the receptor for the bacterial protein flagellin is expressed only on the basolateral surface of intestinal epithelial cells,[3] meaning that immune responses are mounted only against bacteria that find themselves on the wrong side of the epithelial barrier.

The purpose of these mechanisms is clear: prevent strong immune reactions against our resident microbes. In addition to protecting us against harmful pathogens, these bacteria harvest energy from our food and provide us with nutrients that would otherwise be inaccessible. For example, several bacterial species in the large intestine ferment carbohydrates that cannot be digested by the host, and convert them into short-chain fatty acids which can be assimilated.[4] However, the array of fermentation products produced from food is vast and several products produced from proteins have toxic properties associated with colon cancer and inflammatory bowel disease.[5,6] Diet appears to be the crucial factor that determines the balance between the good and the bad.

The composition of the microbiota also affects human health. One of the most striking examples

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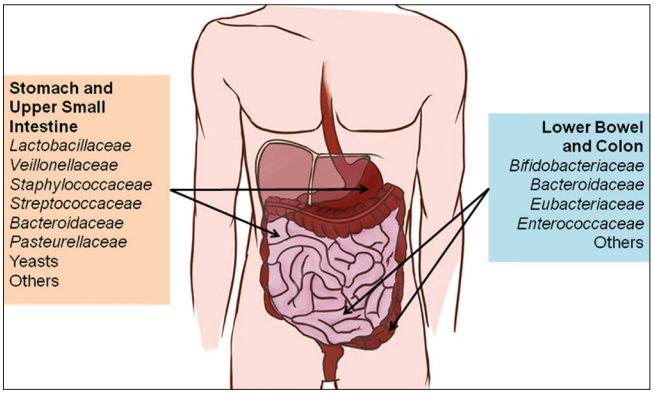

Figure 1: The gut microbiota contains approximately 1014 bacteria, weighs 1–2 kg, and comprises 6–10 major phyla and about 3000 species.[34] Its composition varies along the length of the intestinal tract, with the large intestine and lower bowel containing a larger and more diverse number of bacteria. This figure was kindly provided by Prof. Hsih-Chih Lai.

to date is the balancing act between two major groups of bacteria – Bacteroidetes and Firmicutes – which influence obesity. Fat mice and humans have a higher ratio of Firmicutes to Bacteroidetes in their bowels,[7] and the transfer of microbiota from fat mice to germ-free mice is sufficient to transfer the obese phenotype.[8] Interventions that affect the composition of the microbiota may positively influence human health, and probiotics, which are live cultures of "beneficial" bacteria, have been marketed for many years. The more drastic intervention of "fecal bacteriotherapy," which involves accepting a transplant of someone else's stool, has already been successfully applied to treat antibiotic-refractory *Clostridium difficile* infection.[9]

Thus, we can consider the microbiota as a separate organ, whose normal functioning is essential for human health. We will no doubt continue to be surprised by the influence of this alliance between man and microbe.

SPOTLIGHT ON ORIGINAL ARTICLES – Antioxidants Protect Against Damage to Normal Tissues in Irradiated Mice

The success of radiotherapy depends not only on its ability to kill cancer cells but also on its avoidance of healthy tissue. In this issue of the *Biomedical Journal*, Patil and colleagues report that the antioxidants rutin (RUT) and quercetin (QRT) protect mice from DNA damage induced by ionizing radiation.[10]

In a recent issue, the *Biomedical Journal* published a special report on dietary antioxidants.[11] We saw that the health benefits of these molecules remain controversial and their effects are probably context specific.[12] Nonetheless, many have been praised for their neuroprotective, anti-inflammatory, and anti-cancer properties.[13-15] These properties have been largely attributed to the ability of antioxidants to mop up free radicals which cause major damage to proteins and DNA. Radiotherapy generates copious amounts of hydroxyl free radicals through the action of radiation on water which makes up around 80% of human tissues.[16] Many antioxidants have been shown to limit the toxicity of radiotherapy in animal models.[17] Here, Patil and colleagues investigated the radioprotective effect of two antioxidants, RUT and QRT, in mice.

They fed mice with various doses of RUT or QRT once a day for five consecutive days. They then exposed mice to 3 Gy of gamma radiation on the fifth day and measured DNA damage in bone marrow cells with several cytogenetic and molecular tests. Gamma irradiation led to significantly fewer cytogenetic abnormalities in bone marrow cells from mice pre-treated with RUT or QRT than in those from untreated mice. Furthermore, pre-treatment of mice with these flavonoid compounds limited the formation of micronuclei in red blood cells. Finally, comet assays, which detect DNA damage from changes in the migration of DNA on gel electrophoresis, revealed that DNA damage was more severe after irradiation in blood cells from untreated mice than in those from mice pre-treated with RUT or QRT.

Thus, the results of these tests were unanimous: pretreatment of mice with RUT or QRT protects them from the genotoxic effects of ionizing radiation. These findings build upon previous reports from the same laboratory showing that RUT and QRT inhibit the accumulation of various free radicals in irradiated animals and promote radiation tolerance.[18,19] There is hope that antioxidants from dietary sources could protect patients from the chronic toxicities of radiotherapy. Many hurdles remain, however, and clinical trials with antioxidants have produced mixed results.[17] A remaining challenge is to target the protective effects of antioxidants to normal tissues. The sulfhydryl compound amifostine, which is currently the only radioprotector compound in clinical use, does this quite well already, as it concentrates more rapidly in normal than in tumor cells.[20] Hopefully, further research into the antigenotoxic effects of antioxidants will result in the introduction of new radioprotector compounds that will make radiotherapy more tolerable and, thus, increase patient compliance and the quality of life.

ALSO IN THIS ISSUE: REVIEWS – The Double Life of Activation-Induced Cytidine Deaminase

In this review,[21] Chaudhuri and colleagues discuss the dual function of activation-induced cytidine deaminase (AID), which, by virtue of its deaminating activity at cytidine residues, plays a key role in controlling B cell diversification

and patterns of DNA methylation. These seemingly disparate functions have a common mechanistic basis.

The Extracellular Activities of ATP in Erythrocyte Infection and Disease

Adenosine 5' triphosphate (ATP) is best known as the cell's universal currency of energy, but it also has a lesser known function as an extracellular signaling molecule. Red blood cells release ATP when stressed and this leads to vasodilation. Here, Ramdani and Langsley discuss the negative implications of this activity in the context of malaria and sickle cell anemia.[22]

ORIGINAL ARTICLES – Glucose and the Il-12 Response in Patients with Type 2 Diabetes

In this report,[23] Chu and colleagues examine IL-12 responses in peripheral blood mononuclear cells (PMBCs) from patients with type 2 diabetes and show that changes in *IL-12* gene expression and not osmolarity account for the glucose-mediated up-regulation of IL-12 production.

Plant Extract Kills Prostate Cancers Cells by Apoptosis

Shahneh and colleagues show that extracts from *Echinophora platyloba*,[24] which is used in traditional medicine and even in food in some parts of the world, induce apoptosis in a prostate cancer cell line, but leave HUVEC cells relatively unscathed. These findings suggest that *E. platyloba* contains active compound(s) useful for chemotherapy.

Early Treatment with "Unpopular" Antibiotic Eliminates Multidrug-Resistant Bacteria

Multidrug-resistant *Acinetobacter baumannii* (MDRAB) is an increasing global menace and alternative antibiotics are required to tackle infections involving these bacteria. The antibiotic colistin fell out of favor due to its associated nephrotoxicity,[25] but here, Chen and coworkers show that the safer,[26] aerosolized delivery of colistin can successfully treat MDRAB respiratory tract infections if provided early enough.

Benefit of Rituximab for Patients with Primary Breast Lymphoma Questioned by Taiwanese Study

Primary breast lymphoma (PBL) is a rare type of lymphoma. Ou and coworkers examined the fate of patients diagnosed with PBL in a single Taiwanese hospital over a period spanning almost three decades and found that additional treatment with the widely used monoclonal antibody rituximab did not improve the 5-year overall survival.[27]

Clinicians Urged to Step up the Attack Against *Helicobacter Pylori* Infections

Although *H. pylori* lives fairly inconspicuously in the gut of many infected individuals, it is linked to several diseases.[28] Levofloxacin-containing triple therapy is recommended as a second-line treatment, but concerns have been raised about its effectiveness in 7-day treatment regimens, which are still prescribed by many doctors in Taiwan.[29] Here, Liang and colleagues show that *H. pylori* is eradicated in only 81% of patients who complete the 7-day treatment regimens.[30] Their take-home message: treatment should be extended to 10–14 days or replaced with other antibiotics.

Micronutrients as Biomarkers for Oral Cancer

Baharvand and coworkers show that the serum levels of ferritin,[31] copper, and zinc are significantly higher in patients with oral cancer than in healthy controls. Such alterations to micronutrients, which have been observed in other types of cancer, may facilitate early diagnosis and may even predict prognosis.[32]

CORRESPONDENCE – Television Viewing and Obesity Among Children

In this correspondence, Kapil and Bhadoria discuss several studies that have linked television viewing to childhood obesity.[33] Old habits die hard it would seem, as the amount of television watched by young children is predictive of body mass index (BMI) in later years of life. The authors conclude with recommendations from the *American Academy of Pediatrics*: Total media time for children (television, video, and video games) should be limited to 1–2 h of quality programming per day.

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