B cell lymphoma and the microbiome

By Kai-Jye Lou, Senior Writer

A key challenge in mining the microbiome for therapeutic strategies has been to characterize the functional role of specific bacterial populations in the context of a disease. Now, University of California researchers have shown the gut microbiome is a key contributor to lymphoma risk and identified specific alterations to microbiome composition that could potentially attenuate this risk.¹

The UC researchers are sifting through a set of bacterial species to identify those that could be used as probiotics or targeted to alter disease phenotypes, and have founded **Microbio Pharma Inc.** to develop and commercialize resulting products.

For more than a decade, Robert Schiestl has been using lymphoma-prone, *ataxia telangiectasia mutated (Atm)* knockout mice to study mechanisms that drive carcinogenesis.

Schiestl is a professor in the departments of pathology and laboratory medicine, environmental health sciences, and radiation oncology at the **University of California, Los Angeles**.

Ataxia telangiectasia is an autosomal recessive neurodegenerative disorder

caused by mutations in *ATM*, which has roles in cell cycle control and DNA repair. In addition to neuromuscular and immune system deficits, patients with the condition also have a high risk of developing hematological malignancies, and the majority of those cases are B cell lymphomas.²

Researchers from Schiestl's lab and others have found large disparities among different types of *Atm*-knockout mice in the time to lymphoma onset and median lifespan.³⁻⁵ The mechanistic underpinnings of these disparities were unclear.

After ruling out genetic diversity as the culprit, Schiestl's group sought to determine whether environmental factors such as housing conditions and diet could be responsible for the differences. In 2006, the group reported that *Atm*-knockout mice housed in sterile conditions had delayed lymphoma onset and much longer lifespans than those housed in nonsterile conditions.⁶

That result suggested the culprit could be microbial in origin.

In the current study, Schiestl's group sought to determine the specific microbes responsible for the differences in disease latency and lifespan in the *Atm*-knockout mice.

In *Atm*-knockout mice from colonies housed under sterile conditions, genetic instability decreased and lymphoma latency and lifespans increased gradually from one generation to the next. Compared with *Atm*-knockout mice housed under nonsterile conditions, those housed under sterile conditions had less genetic instability and longer lymphoma latency and lifespans.

The researchers ruled out external microbial sources as the culprit because the benefits were transmissible in mice housed under sterile conditions. Thus, Schiestl looked at internal microbial sources—namely the gut microbiome.

Indeed, multiple recent studies have linked dysregulation of the gut microbiome to various cancers, including those outside the gastrointestinal system.⁷⁻¹¹

Analysis of fecal pellets showed the gut microbiome in *Atm*-knockout mice housed under sterile conditions had less diversity and different dominant bacterial species than the more conventional microbiome of those housed under nonsterile conditions.

To confirm microbiome differences were responsible, the researchers used the same parental mouse strain to establish two colonies of *Atm*-knockout mice—each with one of the distinct gut microbiome phenotypes. The two mouse colonies recapitulated the differences in genetic instability and lifespans seen in mice housed under sterile and nonsterile conditions.

Additional microbiome profiling of these two mouse colonies showed that one of the most prominent differences was increased abundance of *Lactobacillus johnsonii* in the restricted gut microbiome compared with the more diverse, conventional microbiome.

In *Atm*-knockout mice harboring the more diverse microbiome, oral administration of *L. johnsonii* decreased multiple markers of lymphoma risk such as oxidative stress, DNA damage, systemic inflammation and micronucleus formation compared with saline.

Results were published in *Cancer Research* and included authors at the **University of California, Riverside**.

"The data, in a correlative way, link differences in the microbiota with systemic oxidation state, inflammation and genotoxicity," said Giorgio Trinchieri, director of the cancer and inflammation program and chief of the laboratory of experimental immunology at the **National Cancer Institute**. "This is a novel and important result that opens the way for more targeted and mechanistic studies to analyze the specific role of bacterial species and their mechanism of action."

Revealing relevant bacteria

Schiestl said the studies have yielded a repertoire of bacterial species that vary between the two gut microbiome profiles. His group now is evaluating how changing individual bacterial populations affects the disease phenotype in *Atm*-knockout mice.

"We are inoculating our mice with these bacterial strains one by one to see if and how we change the disease phenotype," he told *SciBX*.

Schiestl said one group of gut bacteria that deserves extra scrutiny

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is *Helicobacter*. “In addition to *H. pylori*, which are already linked to intestinal inflammation and cancer, we found five other *Helicobacter* species that are more prevalent in the conventional microbiomes than in the less diverse, restricted microbiomes,” he noted.

Because the current study only evaluated the effects of *L. johnsonii* supplementation on markers of lymphoma risk in the *Atm*-knockout mice, Schiestl said his group still needs to run studies to show the direct effect *L. johnsonii* supplementation has on lymphoma onset and lifespan.

Trinchieri wanted to see more comprehensive studies to elucidate the underlying mechanisms and to determine how much of the mouse data will translate into humans.

“Better understanding of the molecular mechanisms in the

mouse system and analysis of the contribution of different bacterial species and their effector molecules should be the objective of future studies,” he told *SciBX*.

In terms of therapeutic strategies, Schiestl noted that oral supplementation with bacterial species identified as beneficial and development of compounds that selectively kill off bacterial species identified as harmful are possible approaches but declined to provide details.

Compounds to selectively kill specific bacterial populations include narrow-spectrum antibiotics and bacteriophages. The latter can be freeze-dried and turned into pills without losing efficiency, and phage-based products such as **Intralytix Inc.**’s ListShield and SalmoFresh have ‘generally recognized as safe’ (GRAS) status from **FDA**.

ListShield is a blend of phages that target and kill specific pathogenic strains of *Listeria monocytogenes*. SalmoFresh is a blend of phages that target and kill *Salmonella enterica*. Intralytix markets both as products to decrease food contamination and prevent food-borne illnesses.

Schiestl said the group plans to develop probiotic products based on its research and commercialize them through Microbio Pharma.

Trinchieri agreed that supplementation strategies could temporarily alter the gut microbiome, but thinks permanent changes may be more difficult to achieve. Moreover, he cautioned that changing the gut microbiome, particularly by adding individual bacterial species, may alter the equilibrium of the commensal population and have effects that are difficult to predict.

The Regents of the University of California have multiple pending patents that cover the findings described in the *Cancer Research* paper. Schiestl said he should be contacted directly for potential partnership and/or investment opportunities.

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COMPANIES AND INSTITUTIONS MENTIONED

Intralytix Inc., Baltimore, Md.
Microbio Pharma Inc., Los Angeles, Calif.
National Cancer Institute, Bethesda, Md.
University of California, Los Angeles, Los Angeles, Calif.
University of California, Riverside, Riverside, Calif.
Food and Drug Administration, Silver Spring, Md.

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