



How microbes are rewriting the rules of immunity

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ABOUT THE LECTURE

Microbes aren't just passive passengers in our bodies—they're active participants in shaping our immune system and health. In this Front Row lecture, Scripps Research professor Howard Hang shared how his lab is using chemistry, microbiology and immunology to decode the complex language between human cells and the trillions of microbes that live in and on us. By identifying specific microbial species and the molecules they produce, Hang's work is paving the way for novel therapies to combat infections, cancer and inflammatory disease.

TOP TAKEAWAY POINTS

- Microbial communities (collectively known as the microbiome) living in the gut produce small molecules called metabolites that can directly influence immune responses, from protecting against infection to shaping the body's reaction to cancer therapies. This means the trillions of microbes inside us aren't just along for the ride; they actively shape how our immune system detects threats and responds to disease.
- Hang's lab identified SagA, an enzyme secreted by the bacterium *Enterococcus faecium* that cuts bacterial cell wall fragments into small immune-stimulating pieces. These fragments—known as muropeptides—activate host immune receptors, effectively priming the immune system for action. Notably, mice pre-treated with SagA-expressing bacteria become more resilient to *Clostridium difficile* infections, a leading cause of colon inflammation after antibiotic use.
- The microbiome might explain who benefits from cancer immunotherapy. Certain gut microbes, including *E. faecium*, are more abundant in patients who respond well to immune-based cancer drugs known as checkpoint inhibitors, which help the body's own defenses attack tumors. In preclinical models, Hang's team showed that SagA not only protects against infection but also boosts the immune system's ability to recognize and target tumor cells when paired with immunotherapy.
- Hang and his team also found that probiotics can be reprogrammed to enhance cancer immunotherapy. To safely harness the benefits of SagA without introducing potentially drug-resistant bacteria, the researchers engineered the probiotic *Lactococcus lactis* to produce the enzyme. This synthetic strain was shown to improve responses to checkpoint inhibitors in preclinical models. Now known as R-5780 in its advance through clinical trials, the strain represents a promising new tool in microbiome-based cancer treatment—and because *L. lactis* is already used in food production, it offers a safe, scalable delivery platform.
- Hang's lab is developing specialized tools to track how microbial metabolites interact with human proteins and immune-related pathways. These tools allow researchers to identify which bacterial molecules trigger immune responses, and to observe how the molecules alter cellular communication during inflammation or disease. This approach is also uncovering the hidden links between the microbiome and other biological functions like metabolism and brain health, expanding the potential for microbiome-informed therapies across many diseases.

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