

PRIZE ESSAY

TRANSLATIONAL MEDICINE

Microbiome dynamics in obesity

The microbiome influences central features of metabolic disease

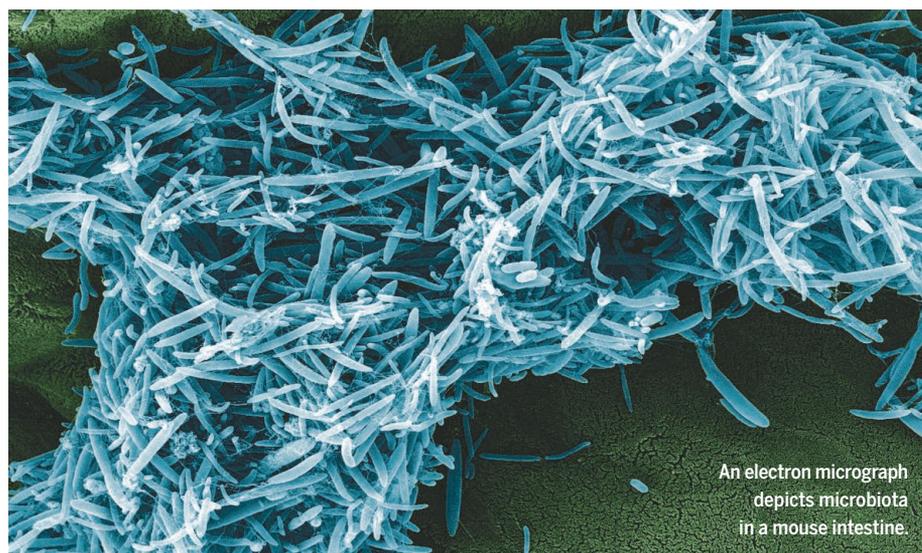
By Christoph A. Thaiss

The prevalence of obesity has increased at an astounding rate over the past decades. More than 44% of the global population is estimated to be overweight, and more than 300 million individuals are affected by morbid adiposity (1). Obesity is a major risk factor for a number of co-occurring diseases, including type II diabetes mellitus, nonalcoholic fatty liver disease, and ischemic cardiovascular disease (2). Thus, the obesity pandemic has far-reaching consequences on life expectancy, quality of life, and health-care costs.

What has caused this rapid increase in obesity within less than a generation? The past century has seen dramatic changes in human lifestyle, ranging from new dietary patterns to improved hygiene and altered sleep-wake cycles. However, the molecular and cellular mechanisms by which these environmental factors predispose humans to obesity remain largely unknown. As a graduate student in Eran Elinav's laboratory at the Weizmann Institute of Science, I investigated three phenomena of human obesity that are tightly linked to the modern human lifestyle. For all three, we discovered an unexpected role for temporal and spatial dynamics of the intestinal microbiome—the community of trillions of microorganisms that inhabit the gastrointestinal tract (see the figure).

CIRCADIAN REGULATION OF MICROBIOME OSCILLATIONS

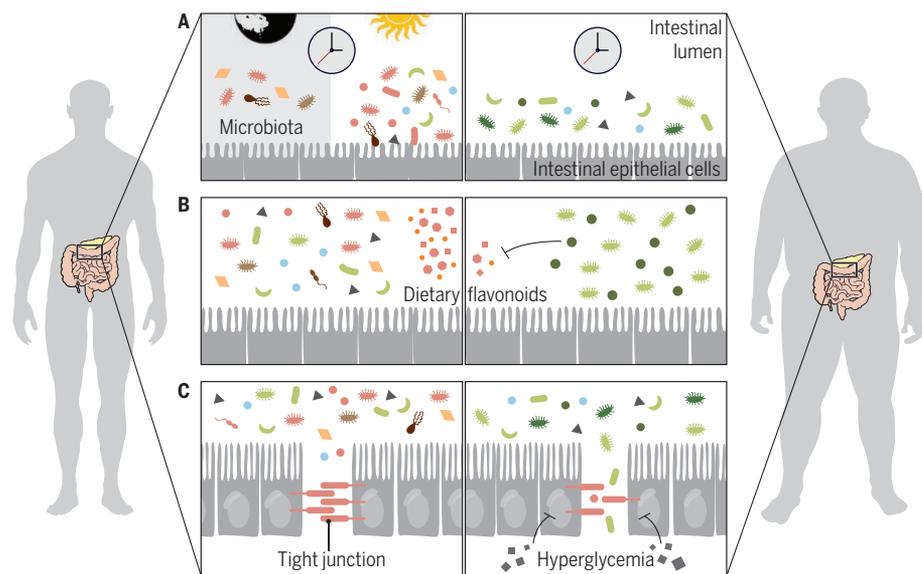
The body's circadian clock evolved in most species to adjust the organism's physiology to the daily environmental fluctuations that are caused by Earth's rotation on its axis (3). Disruption of the circadian clock—by shift work, frequent jet lag, or exposure



An electron micrograph depicts microbiota in a mouse intestine.

Temporal and spatial microbiome dynamics in obesity

(A) The microbiome undergoes oscillations in composition, functional activity, and localization over the course of a day. These diurnal patterns are aberrant in obesity. (B) The obesity-associated microbiota degrade diet-derived flavonoids, thereby diminishing energy expenditure of the host and predisposing it to accelerated weight gain after successful dieting. (C) Hyperglycemia disrupts epithelial barrier function and facilitates the influx of microbiota-derived products into the systemic circulation, thereby driving chronic inflammation.



to artificial light during the night—is a widespread consequence of the modern human lifestyle. Epidemiologically and experimentally, clock disturbances have been linked to metabolic diseases, including obesity and hyperglycemia (4, 5).

In our initial experiments, we discovered that the gut microbiome in both mice and humans undergoes oscillations in a 24-hour rhythm (6). These diurnal fluctuations encompass multiple characteristics of the microbiota, such as taxonomic composition, metagenomic function, metabolite

secretion, and biogeographical localization within the intestine.

We then showed that daily oscillations in the intestinal microbial community influence the circadian biology of the host, by determining the oscillatory pattern of serum polyamines. These, in turn, orchestrate the circadian transcriptional program in metabolic tissues (7). The host-microbiome interface can thus be viewed as a dynamic interplay that undergoes hour-scale fluctuations over the course of a day. Aberrations in this coordinated daily interplay may contribute to the development of obesity and its complications.

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**GRAND PRIZE WINNER:
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MEDICINE**

Christoph A. Thaiss

Christoph A. Thaiss performed his undergraduate studies at the University of Bonn, Yale University, and ETH Zurich, and received his Ph.D. in immunology from the Weizmann Institute of Science in Rehovot, Israel. After the completion of his graduate studies, he became an assistant professor at the Perelman School of Medicine at the University of Pennsylvania. His lab studies environmental impacts on metabolic and inflammatory diseases.



**FINALIST: ECOLOGY
AND ENVIRONMENT**

Matthew Savoca

Matthew Savoca received his undergraduate degree from Cornell University and his Ph.D. in Ecology from the University of California, Davis. He is currently a postdoctoral researcher at the Hopkins Marine Station of Stanford University studying the foraging behavior of baleen whales and their possible interactions with plastic debris.

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**FINALIST: CELL AND
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Ruixue Wan received her undergraduate degree from Sun Yat-sen University in Guangzhou, China and her Ph.D. from Tsinghua University

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**FINALIST: GENOMICS
AND PROTEOMICS**

Tim Wang

Tim Wang received his undergraduate degree from the University of California, Berkeley, and his Ph.D. from the Massachusetts Institute of

Technology. He is currently investigating the structural and functional organization of neocortical circuits as a postdoctoral fellow at the Janelia Research Campus in the laboratory of K. Svoboda.

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We found that disruption of host circadian rhythmicity, either genetically or by jet lag, provokes the development of an altered microbial community whose properties predispose the host to obesity and glucose intolerance (6). Circadian rhythms, it seems, are a new principle in host-microbiome interactions with a profound impact on metabolism.

MICROBIOME “MEMORY” IN RECURRENT OBESITY

We also investigated microbiome dynamics on larger time scales. One of the biggest conundrums in the clinical management of obesity is the rapid weight regain of formerly obese individuals after successful weight loss, a phenomenon commonly known as the “yo-yo effect” of recurrent obesity.

We found, in mice, that a period of obesity induced long-lasting alterations in the composition of the microbiome that persisted even after the host organism returned to normal weight (8). This “memory-like” behavior of the microbiome mediated the susceptibility of the formerly obese host to accelerated weight regain.

The weight-modulating effect of the microbiome was achieved by the degradation of dietary flavonoids, which resulted in reduced metabolic activity of adipose tissue and diminished energy expenditure. When we restored flavonoid levels, energy expenditure was normalized, and weight regain was ameliorated. Manipulation of the microbiota and intestinal metabolites as a means of achieving and maintaining weight loss is now being tested in humans.

MICROBIOME INVASION FACILITATED BY HYPERGLYCEMIA

The third phenomenon we addressed is the enhanced susceptibility of obese and diabetic individuals to enteric infection and systemic inflammation. Intestinal epithelial cells normally provide a tight barrier that separates intestinal bacteria from the systemic circulation.

In analyses of obese and diabetic mice, we found that chronic hyperglycemia led to a breakdown of the epithelial barrier and facilitated translocation of intestinal bacterial components into the bloodstream, where they promoted systemic inflammation (9). The detrimental effect of chronically high levels of glucose was mediated by functional reprogramming of epithelial metabolism and transcription. These cellular alterations compromised

the assembly of tight junction complexes, which are critical for the maintenance of an intact barrier.

We validated these findings in a human cohort, in which chronic hyperglycemia strongly correlated with the amount of microbial products detected in the circulation. These findings suggest a mechanism linking obesity with an enhanced risk for mucosal infection and systemic inflammation. They also suggest that glycemic control may be critically important to achieve local containment of the intestinal microbiota in diabetic individuals.

TOWARD A POSTBIOTIC FUTURE

My Ph.D. work highlights temporal and spatial microbiome dynamics as an important element of host-microbiome interactions in obesity. We hypothesize that alterations in this dynamic interplay are centrally involved in the impact of the modern human lifestyle on the development of obesity and associated comorbidities.

A common theme emerging from the three features discussed above is that the impact of the microbiome on human health and disease is largely mediated by the exchange of metabolites (for example, polyamines act on the circadian clock, flavonoids on adipose tissue, and glucose on intestinal epithelial cells). As such, this work provides evidence for a powerful new therapeutic concept, which—rather than interfering with the intestinal microbial community itself (via prebiotics and probiotics)—may be based on the modulation of intestinal metabolites with a direct effect on host metabolism (analogously termed “postbiotics”) (10, 11). Exploring the postbiotic universe of microbiota-derived metabolites that modulate host physiology may yield interesting insights, enabling us to understand and, indeed, counteract the rapid rise of obesity worldwide. ■

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