time, they were able to measure the energy spectrum of the resonant mode inside the cavity with a resolution of microelectronvolts. By using only a few tens of milliwatts of optical power, they broadened the spectrum of electron energies produced by the electron microscope by around 400 eV.

The interactions with photons endow these phase-modulated electron waves with special properties. After interacting with the light field and then dispersing through a vacuum in the device, electrons with higher momenta catch up with slower electrons. When this happens, the electrons cease to propagate as a single continuous beam, and instead form short pulses lasting less than one femtosecond, separated by the period of the optical wave[1]. These modulated electron beams enable attosecond metrology (1 as is 10^{-18} s) and experiments that can probe ultrafast electronic dynamics with high spatial resolution.

In the past year, the behaviour of these modified electron beams has been studied theoretically, and several predictions have been made — including how they will interact with systems existing in two independent quantum states[10], and how the coherence of the electron beam (the degree to which the waves are in phase with each other) could be transferred to photons emitted through a process known as cathodoluminescence[11]. Henke and colleagues' results offer a way of investigating these phenomena experimentally, which might enable control of optical excitations with the nanometre resolution provided by electron microscopes. It also puts forward a means of achieving high electron current, even in experiments with electron beams characterized by narrow energy spectra[12] — thereby opening a route for simultaneous high-resolution spectroscopy, microscopy and quantum control in the near future.

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Gut clues to weight gain after quitting smoking

Research has uncovered factors that underlie the weight gain associated with cessation of smoking. Here, scientists consider the implications of this finding from the perspectives of gut biology and of smoking. **See p.713**

The paper in brief

- **People who stop smoking usually go on to gain weight, which can cause some individuals to start smoking again.**
- **The factors underlying this type of weight gain are not fully understood.**
- **Microorganisms in the gut (termed the microbiota) can influence aspects of human health, and have been implicated in obesity.**
- **On page 713, Fluhr *et al.*[1] report evidence from studies in mice and humans that point to the microbiota as having a role in weight gain associated with the cessation of smoking.**
- **These findings might aid efforts to enable people to avoid side effects associated with quitting smoking.**

Matthew P. Spindler & Jeremiah J. Faith

Gut microbial mischief

Cigarette smoking is the leading preventable cause of death worldwide, and yet many smokers never attempt to quit[2,3]. The weight gain associated with cessation of smoking is cited as a major reason why more people don't try to stop[2,3]. This weight gain is broadly attributed to smoking-associated effects on energy intake, metabolic rate and physical activity, but the specific underlying molecular mechanisms are not understood. Fluhr and colleagues now provide evidence that implicates gut microorganisms in this phenomenon.

The authors established a mouse model that replicates features of the weight change that occurs after smoking cessation in humans. These animals gained less weight during smoke exposure, and their weight returned to the non-smoking baseline after exposure ceased. The authors demonstrate that microbiota-dependent factors affect how much weight is regained. They found that administering antibiotics reduced the amount of weight regained, which suggests that a bacterial component of the microbiota targeted by antibiotics contributes to the process. This effect on the animals' weight was maintained for weeks after antibiotic administration was halted, and the results were unaffected by changes in diet or differences in the original microbiota of mice obtained from various vendors.

Fluhr and colleagues then carried out experiments to pinpoint the effect of smoke-associated microbiotas on weight change. Mice that lacked their natural microbiota (germ-free animals) and that received a transplant of faecal microbiota from mice exposed to smoke gained more weight than did animals transplanted with control microbiotas from mice not exposed to smoke. This type of weight gain was observed consistently for two recipient strains of mice lacking their natural microbiota and on two different diets, suggesting that smoke-associated microbiotas directly affect weight gain.

However, several aspects remain to be addressed before these observations can be generalized to humans. Studies in humans that compare the microbiota of smokers and non-smokers have yielded disparate results — some research indicates that the microbiota is perturbed, whereas other studies find no difference[4–6]. Fluhr and colleagues show that the microbial composition of faeces differs between mice exposed to smoke and unexposed mice, but such a distinction is less clear in human studies. Furthermore, the community of bacteria that make up the microbiota varies tremendously between individuals. Experiments establishing whether the microbiota-dependent modulation of this

weight-loss phenomenon is robust, despite the interpersonal variability of the human microbiota, would provide much-needed insight into the generalizability of these observations. To gather such data, one could perform a retrospective analysis of clinical data to assess whether weight changes in recipients who received faecal-microbiota transplants from smoking donors differed from weight changes in those who received transplants from non-smoking donors.

Groups of people in the population who are most at risk of greater weight gain after quitting smoking include women; those on a low income or with a poor diet; people whose physical activity is limited; and those who have been heavy tobacco users[3,4]. It is therefore worth noting that although insights using simple model systems can revolutionize how we think about the weight gain associated with the cessation of smoking, efforts to extend these insights from models to clinical practice should take into consideration the complex interplay of factors that influence individual behaviour linked to lifestyle modifications.

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Junshi Wang & Paul J. Kenny
Smoke clears on weight gain

The saying, 'you are what you eat' implies that what we consume influences our health. Fluhr and colleagues' results go one step further by suggesting that cigarette smoke can also have an effect, acting on the gut microbiota to facilitate the extraction of energy from our food.

Tobacco smokers tend to have lower body weights than non-smokers, a situation that is reversed when smokers quit the habit[7]. Concerns about weight gain discourage many smokers from quitting, which in turn increases their risk of developing smoking-related diseases.

Nicotine is the major reinforcing component of tobacco that drives the smoking habit[8]. It stimulates nicotinic acetylcholine receptors (nAChRs) located on cells that function in reward circuits in the brain to motivate tobacco use[9]. Nicotine also stimulates nAChRs on pro-opiomelanocortin neurons and other appetite-suppressing neurons in a brain region called the hypothalamus to suppress food intake[10]. The general assumption was that the weight gain in ex-smokers is a consequence of the opposite process — decreased activity of these hypothalamic neurons, and perhaps increased activity of pro-feeding circuits in the brain.

However, Fluhr and colleagues show instead that, compared with microbiotas not exposed to tobacco smoke, a microbiota exposed to smoke produces a greater abundance of metabolite molecules that aid the extraction of energy from food by the gut and that promote weight gain on cessation of exposure. Most notably, the molecules associated with this weight gain are derivatives of the amino acid glycine, such as dimethylglycine (DMG). When mice were put on a diet deficient in choline sulfate, a molecule needed for the synthesis of DMG and related compounds, they were less prone to weight gain associated with smoking cessation.

> **"These findings offer possibilities to consider from a therapeutic perspective."**

Unexpectedly, this ability of tobacco smoke to modify the microbiota occurred independently of the nicotine content of the smoke, and the effects on the microbiota were not reproduced if mice were given nicotine instead of being exposed to cigarette smoke. This finding suggests that non-nicotine components of tobacco are responsible for remodelling the gut microbiota to enhance the extraction of energy from food and promote weight gain. It challenges the idea that nAChRs in the hypothalamus and other brain sites involved in maintaining energy homeostasis are solely responsible for the actions of cigarettes on appetite, metabolism and the regulation of body weight.

Fluhr and colleagues' findings have major implications for our understanding of the mechanisms that underlie smoking-related diseases. For example, glycine and certain other amino acids can function as neurotransmitter molecules that aid communication between neurons, or that serve as key precursors in the synthesis of neurotransmitters. Given that cigarette smoke influences the microbiota-mediated production of glycine derivatives, this raises the possibility that these molecules can enter the bloodstream and subsequently gain access to sites in the central nervous system that are involved in appetite regulation and energy metabolism. It is also possible that microbiota-generated inhibitory or excitatory neurotransmitters act in the gut itself to modify the activity of local sensory neurons. This could therefore influence the transmission of information to brain centres involved in energy homeostasis and other processes relevant to tobacco use, such as the desire to smoke.

It is possible that the gut microbiotas of smokers more efficiently harvest not only nutrients, but other substances, too. For example, it will be interesting to discover whether the amounts of nicotine extracted from tobacco smoke, acting in the brain to perpetuate the tobacco habit, or nicotine-derived bioactive molecules (metabolites), are influenced by the gut microbiota or by the microbiota of organs such as the lungs. By extension, the absorption, metabolism and distribution of substances that are often taken together with tobacco products, particularly alcohol, might be affected by the actions of cigarette smoke on the microbiota.

These findings offer possibilities to consider from a therapeutic perspective. Dietary supplements that act in the gut, such as the choline sulfate needed to generate DMG and related glycine derivatives, or precursors of other microbiota-generated bioactive metabolites, might limit weight gain in abstinent smokers and encourage smokers to attempt to quit. Identifying the non-nicotine components of tobacco smoke responsible for remodelling the gut microbiota might permit their removal from cigarettes to lessen weight gain during abstinence. Alternatively, these components might be harnessed for use in individuals who would benefit from enhanced harvesting of nutrients from food, such as those with the cancer-associated weight loss known as cachexia.

This fresh perspective on the weight gain of ex-smokers should encourage closer consideration of whether other smoking-related physiological and behavioural changes involve processes that are not initiated in the brain.

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