

examined cells lacking different combinations of HP1 isoforms, they found that all three had to be deleted to mimic the effects of ADNP mutation on gene expression. This indicates that the three HP1 proteins are functionally redundant — that is, they can compensate for one another in ChAHP.

Why might ADNP preferentially interact with HP1 γ and HP1 β ? HP1 α has an amino-terminal region, unique among HP1 proteins, through which it promotes the self-organization of heterochromatin into liquid-like droplets⁷. This process, called phase separation, probably minimizes interactions with other nuclear proteins, maintaining the condensed state of heterochromatin. However, ChAHP-mediated silencing of euchromatic genes must be reversible to enable genes to respond to differentiation cues during development, perhaps making phase separation less desirable at these genomic regions.

HP1 proteins interact with PXVXL-containing factors such as ADNP through a carboxy-terminal 'chromoshadow' domain. But in heterochromatin, HP1 binds histone H3 through an evolutionarily conserved amino-terminal chromodomain⁸, at sites where the histone is tagged by methyl groups on amino-acid residue lysine 9 — a chemical modification dubbed H3K9me3. It is through this interaction that HP1 proteins induce chromatin condensation. Might H3K9me3 also promote HP1 binding at ChAHP-bound regions? In favour of this hypothesis, HP1 can recruit ADNP to H3K9me3-marked heterochromatin³. However, Ostapcuk and colleagues show that ChAHP can efficiently bind to its DNA targets even if HP1 is engineered to lack its chromodomain. Furthermore, regulatory sequences bound by ChAHP lacked H3K9me3. Therefore, H3K9me3 is unlikely to have a role in ChAHP-mediated transcriptional silencing.

People with Helsmoortel–Van der Aa syndrome generally have ADNP mutations that produce a truncated protein lacking the DNA-binding domain and the PXVXL motif⁹. To investigate whether this mutation disrupts ChAHP-complex formation, Ostapcuk *et al.* expressed one such patient-derived mutant protein in mouse ES cells. The mutant ADNP failed to bind to HP1 β or HP1 γ , and genes normally bound by ChAHP were aberrantly expressed. Furthermore, analysis of chromatin accessibility in ADNP-deficient ES cells revealed that the mutation led to opening of chromatin in regions immediately flanking ADNP-binding sites.

Together, Ostapcuk and colleagues' findings demonstrate that ChAHP does not generate broad swathes of heterochromatin, as observed at H3K9me3-marked regions bound by HP1. Instead, the complex generates focused regions of condensed chromatin that inhibit the transcription of differentiation-promoting genes. Aberrant expression of such genes in the absence of the ChAHP complex

is probably a crucial factor in the aetiology of Helsmoortel–Van der Aa syndrome (Fig. 1).

Although Ostapcuk and co-workers' study focused on the interplay between ADNP, CHD4 and HP1, the researchers found many fewer genes upregulated in mouse ES cells lacking ADNP than in those lacking all three HP1 isoforms. And, consistent with previous reports^{10,11}, the authors' analysis of HP1-interacting proteins revealed a plethora of overlapping and isoform-specific binding partners, many of which have DNA-binding activity. Notably, mutations in several of these HP1-interacting transcription factors are implicated in other rare syndromes associated with intellectual disability, including in genes that encode the proteins AHDC1 (ref. 12), CHAMP1 (ref. 13) and POGZ (ref. 14). Thus, it is tempting to speculate that HP1 proteins act as co-repressors for many as-yet-undescribed DNA-binding complexes that regulate the expression of distinct gene sets.

Ostapcuk and co-workers' study has revealed a key mechanism of HP1 recruitment to chromatin. Their work sets the stage for future studies on the broader role of this enigmatic co-repressor in gene regulation and local chromatin compaction. ■

QUANTUM PHYSICS

Molecular dynamics simulated by photons

The microscopic behaviour of molecules can be difficult to model using ordinary computers because it is governed by quantum physics. A photonic chip provides a versatile platform for simulating such behaviour. [SEE ARTICLE P.660](#)

FABIEN GATTI

Quantum-computing devices could one day outperform ordinary computers, particularly in the simulation of quantum systems. Such devices share their quantum nature with the system to be simulated and are therefore inherently suited to describing quantum phenomena¹. On page 660, Sparrow *et al.*² report a device based on a single photonic chip that can simulate a range of quantum dynamics associated with different molecules. The results are in excellent agreement with simulations carried out by ordinary computers, reaffirming the potential of quantum technology in this area.

In conventional industrial chemistry, the yields of chemical processes are optimized by controlling macroscopic variables, such as temperature and pressure. But the use of high temperatures and pressures wastes a substantial amount of energy and generates unwanted by-products, leading to high energy consumption and pollution. To overcome these issues,

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a promising optimization approach exploits the quantum nature of the reacting molecules.

A central tenet of quantum physics is the superposition principle, which asserts that possible quantum states of a system can be added together and the result will be another possible state. The non-classical aspect of this principle is demonstrated, for example, by quantum bits. These objects can exist in both an on state and an off state at the same time. Such states exhibit quantum coherence, which means that they are correlated in a non-classical way.

The ability to systematically control quantum coherence is considered one of the main challenges in energy science. Such control might enable the synthesis of highly desirable materials and devices, including superfluids (fluids that flow without resistance) and quantum computers. It could also give rise to more-efficient chemical processes than are currently possible.

In conventional chemistry, the quantum states involved in chemical processes are

incoherent. However, coherent superpositions of molecular states can be produced using the light emitted by a laser. The ability to consistently generate these superpositions could improve the efficiency of the corresponding chemical processes and reduce the energy required to control such processes. It might even open up chemical-reaction mechanisms that are otherwise inaccessible^{3,4}.

Laser pulses are the main tool for manipulating molecules in this field. Improvements in the design of these pulses, such as increases in power and tunability, as well as the ability to reduce the duration of the pulses to attosecond (10^{-18} s) timescales, have enabled greater control of light-induced processes in molecules⁵. Since the pioneering work of Ahmed Zewail, who was awarded the 1999 Nobel Prize in Chemistry (see go.nature.com/2idzowq), laser pulses have been used to study quantum coherence in chemistry⁶.

For example, quantum coherence has been used to enhance the rates of chemical reactions in biological systems at room temperature⁷. Such studies conclusively showed that quantum coherence can be partially preserved even in molecular systems open to the external environment⁸.

These experimental advances call for accurate models of the quantum evolution of molecular systems. This is a challenging task for quantum-computing devices, although much progress has been made, thanks to the development of improved algorithms for simulating quantum dynamics^{9,10}.

Sparrow and colleagues engineered a quantum-computing device that is based on a single photonic chip. They used the quantum superposition of photons in the chip to carry quantum information and to model molecular systems. By adjusting the optical circuitry of the chip, the authors simulated a range of quantum dynamics associated with different molecules.

The authors began by simulating vibrational excitations in a variety of four-atom molecules. They then modelled energy transport in the chemical bond of a protein and the transfer of vibrational energy in liquid water. Finally, they tested an algorithm designed to identify quantum states that can lead to the break-up of ammonia. The results of these simulations were in almost perfect agreement with those obtained using ordinary computers.

The first quantum revolution occurred at the turn of the twentieth century, and provided us with the physical laws that govern reality. Sparrow and colleagues have now simulated the time evolution of a quantum superposition of molecular states with the aid of an experimental device that uses the quantum superposition of photons. Such a feat suggests that we could be entering a second quantum revolution, in which the physical laws of nature are used to develop innovative technologies.

Despite these promising prospects, it is not difficult to envisage the problems that follow-up

studies will encounter. In this seminal work, the authors used rather simple molecular models, involving a limited number of mathematical terms. However, this number will increase exponentially when aiming to closely reproduce experimental conditions. Such an increase might dramatically enhance what the authors refer to as the “fundamental errors” in photonics, which include the loss of photons and the loss of quantum coherence.

Nevertheless, Sparrow and colleagues have demonstrated that simulations carried out by quantum-computing devices can be both reliable and efficient, by tackling problems that can be solved using well-established standard techniques. As the authors point out, slight improvements in their method could yield simulations that cannot be achieved using ordinary computers. ■

IMMUNOLOGY

Gut molecules control brain inflammation

Metabolite molecules produced by the gut's microbes activate immune cells in the brain called microglia, which signal to astrocyte cells to mediate responses to inflammation in the central nervous system. SEE LETTER P.724

HARTMUT WEKERLE

Some immunologists regard the central nervous system (CNS) as a no-man's-land, avoided by immune cells and therefore uninteresting. But, in fact, the CNS has a vigorous immune potential that remains dormant in normal conditions but is awakened after injury. The switch that controls the brain's immune microenvironment involves non-neuronal cells called glia — not only microglia, which are sometimes called the immune cells of the CNS, but also multifunctional cells called astrocytes¹. Rothhammer *et al.*² describe on page 724 how these two glial cell types communicate on a molecular level to influence inflammation in the CNS, and show that this interaction is controlled remotely by microbes that inhabit the gut.

A decade ago, the group that performed the current study, along with another research group, discovered^{3,4} an unexpected immunoregulatory role for a ligand-activated transcription factor called the aryl hydrocarbon receptor (AHR), which at the time was best known as a receptor for environmental toxins⁵. The two groups showed that AHR modulates the progression of experimental autoimmune encephalomyelitis (EAE) — an autoimmune disease in mice in which the immune system becomes overactive and attacks the CNS. EAE is often used a model

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of multiple sclerosis (MS). Initially, the groups focused on how AHR might affect EAE by regulating pathogenic and protective subsets of immune cells outside the CNS. But it later emerged that AHR is also strongly expressed in the CNS, particularly in microglia and astrocytes⁶, raising the question of whether AHR in the CNS has a role in autoimmune diseases.

In the current study, Rothhammer *et al.* induced EAE in mice that had been genetically engineered so that AHR could be deleted in microglia (but not in other brain cells or immune cells) by a drug treatment. Elimination of microglial AHR substantially exacerbated EAE in the AHR-depleted mice, but left immune responses outside the CNS unaltered. This finding suggests that AHR activation in microglia inhibits inflammation in the CNS.

Microglia rarely act alone. Instead, they often team up with other cell types to respond to the stimuli that activate them. For example, after being activated, microglia can instruct certain astrocytes to attack local neurons⁷. Rothhammer and colleagues found that AHR-deficient microglia activated by EAE triggered exaggerated inflammatory responses in local astrocytes. Next, the authors used bioinformatics to analyse the gene-expression pathways altered in these glia. This analysis suggested that unexpected proteins signal from microglia to astrocytes.

The usual suspects in such cases are