The authors then went a step further to protect any electronics affixed to the surface of the fabric by ensuring that the sweat was not dispersed across this surface, but instead was repelled to the edges of the device. To do so, they designed a horizontal liquid diode and placed it on top of the vertical liquid diode. The horizontal diode comprised superhydrophilic micropillars that were all identical in shape, but were spatially distributed such that they were sparse near the centre and dense towards the edge. This configuration created a radial surface-energy gradient that guided sweat outwards, even under deformation and after prolonged exposure to sweat.

Zhang *et al.* joined the two liquid diodes together using a ring of polyester fabric that acted as both an adhesive and a sweat collector. This ensured that any electronics integrated into the centre of the substrate would remain unaffected by perspiration, which was pumped automatically to the sweat collector around the edge of the patch. The collected sweat either evaporated into the surrounding environment through the sweat collector or dripped from outlets at the top and edges of the device.

The team demonstrated the versatility of the patch by integrating it with various wearable electronic systems that were connected using detachable magnets. For example, when electrocardiogram (ECG) electronics were incorporated into the patch, it adhered to skin better and showed lower levels of signal interference than did existing ECG patches, providing stable heart-rate readings over the course of a week. The authors also showed that they could integrate an device for electromyography (EMG) — which measures electrical activity in muscles — into the patch.

Zhang *et al.* even demonstrated that their design could be incorporated into a T-shirt embedded with electronics that recorded real-time meteorological parameters, such as temperature — making the garment a wearable weather station. The T-shirt wicked sweat away from the sensors, allowing them to provide accurate readings as the wearer hiked up Hong Kong's Beacon Hill. This suggests that the authors' device will benefit both outdoor enthusiasts and people working in challenging environments. It could even be useful in heavily humid or rainy conditions in future. However, further research will be required to make the current design suitable for such conditions.

Reducing the thickness of the sweat-discharging patch (currently 650 μm) could enhance its wearability further and make it less noticeable to the wearer, especially when it is placed on areas of the body with large curvature or high deformability, such as the joints or the neck. These future improvements aside, Zhang and colleagues' clever integration of two custom-designed liquid diodes is compatible with a range of devices and fabrics, and therefore shows immense promise for developing high-performance wearable patches or smart textiles that contain complex electronic components.

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Memory

Neuronal inflammation makes memories persist

Benjamin A. Kelvington & Ted Abel

A population of neurons that engages mechanisms of the innate immune system during memory formation has been uncovered in mice. Surprisingly, inflammatory signalling might pave the way for long-term memory. **See p.145**

How do memories last? Spanish surrealist Salvador Dalí pondered this question in his famous work *The Persistence of Memory*. He also explored the tragic consequences of memory-loss conditions in *The Disintegration of the Persistence of Memory*. As the global population ages and diagnoses of Alzheimer's disease and related forms of dementia increase, the mechanisms that enable memories to last have captured the attention of neuroscientists. Yet what enables brief experiences, encoded over just seconds, to be replayed again and again during a lifetime remains a mystery. On page 145, Jovasevic and colleagues[1] fit a crucial piece into this puzzle by describing molecular mechanisms that are essential for memory and mark a new population of neurons.

In the 1950s, a man referred to as H.M. had part of his brain's temporal lobes surgically removed in an attempt to treat his epilepsy, but he was left incapable of forming new memories. Since then, scientists have homed in on the hippocampus — one of the areas removed from H.M.'s brain — as a hub for many types of memory[2].

Neuroscientists are now focused on determining how populations of neurons in the hippocampus respond to memory-inducing stimuli. Groundbreaking work has revealed that a population of neurons known as the engram is required for memory formation[3]. Engram neurons are characterized by the expression of a set of genes called immediate early genes, which is rapidly induced after learning. The current work uncovers a population of neurons that instead shows activation of innate immune signalling days after learning (Fig. 1).

Jovasevic and colleagues assessed gene expression in mice after contextual fear conditioning, in which mice learn to associate a small electric shock with a new environment. They compared mice 4 days after conditioning (a recent-memory timepoint) and 21 days after conditioning (a remote-memory timepoint) and found that the hippocampus of mice at the recent-memory timepoint showed signs of inflammation that were indicative of activated signalling by the protein Toll-like receptor 9 (TLR9). TLR9 triggers an innate immune response to DNA in the cell's cytosol that typically results from bacterial pathogens[4]. The authors showed that, in neurons, this inflammation is induced by persistent DNA damage and the release of TLR9-activating DNA fragments from the neuron's own nuclear genome.

Rapid induction of immediate early gene expression is known to require double-strand DNA breaks that are rapidly repaired[5]. However, Jovasevic *et al.* discovered that, in a population of neurons that is mostly distinct from a population expressing the immediate early gene *cFos* (a marker of the engram), DNA

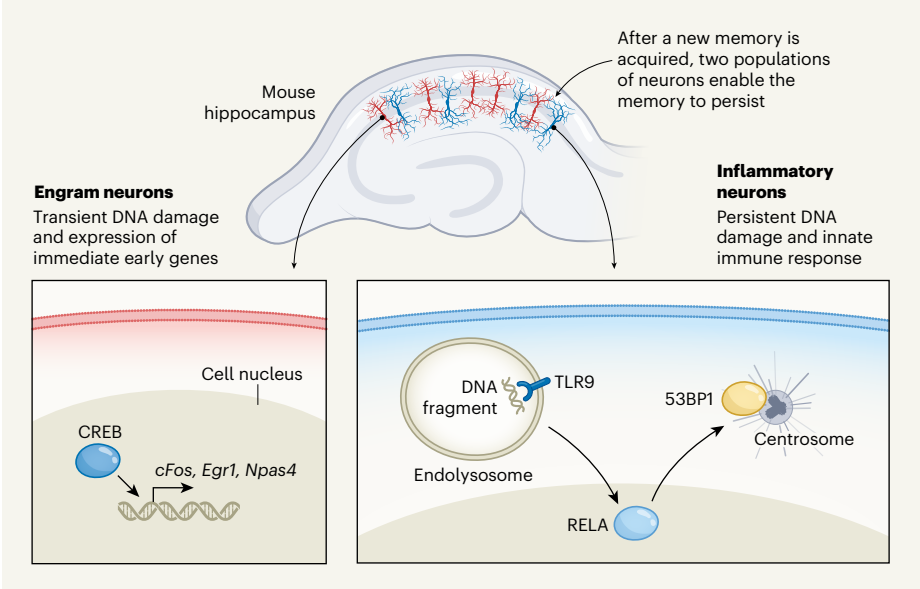

Figure 1 | Neurons that are essential for the formation and persistence of memory. Jovasevic *et al.*[1] investigated neurons in a region of the mouse brain called the hippocampus, which is responsible for memory and learning. Following memory acquisition, neurons belonging to a population known as the engram express a suite of immediate early genes (such as *cFos*, *Egr1* and *Npas4*), a process that is mediated by the transcription factor CREB[8]. This is coupled to transient DNA damage that accompanies neuronal activity[5]. This response is important for the formation of long-term memories[3]. Jovasevic *et al.* uncovered a distinct population of neurons that show an inflammatory response to DNA damage that persists for days after memory acquisition. Inflammatory signalling is mediated by a protein of the innate immune system called TLR9, which detects extra-nuclear fragments of DNA that have been incorporated into cellular compartments called endolysosomes. The authors also found that the transcription factor RELA is needed for damaged DNA to be localized to a cellular structure called the centrosome, where the protein 53BP1 mediates DNA repair. Disrupting these mechanisms results in mice being unable to retrieve fear-associated memories, suggesting that both engram neurons and inflammatory neurons are essential for memories to persist.

damage persists for 4 days. Deleting the *Tlr9* gene from hippocampal neurons, and therefore the innate immune response to extra-nuclear DNA, prevented mice from recalling long-term memories. These results suggest that the sensing of double-strand DNA breaks by TLR9 is a versatile molecular process that is active in both memory and innate immunity.

Crucially, Jovasevic *et al.* provided insights into the mechanisms downstream of TLR9 that lead to memory persistence. The authors observed that, although most double-strand DNA breaks are repaired rapidly, those that persist show a peculiar localization to the centrosome – a cellular structure that is best known for its role in cell division, but that also plays an increasingly appreciated part in the DNA-damage response. DNA localized to the centrosome forms a DNA-damage response complex that also includes the protein 53BP1, a key mediator of double-strand DNA break repair. The authors showed that removing *Tlr9* from hippocampal neurons prevents the accumulation of centrosomal DNA-damage and DNA-repair complexes, suggesting that a key function of TLR9 signalling in neurons is to maintain genome integrity.

The authors also demonstrated that removing a protein called RELA – the most abundant member of the NF-κB family of transcription factors and a key downstream mediator of TLR9-induced inflammatory signalling – interferes with the accumulation of the centrosomal DNA-repair machinery, indicating that RELA connects TLR9 activation to DNA repair by 53BP1. Similar to behavioural memory, immune memory is shaped by experience. A 2022 study of the innate immune response revealed that NF-κB signalling encodes information about both a cell's current state and its history[6]. The similarities between this earlier research and the current work suggest that the molecular mediators of the innate immune response have related memory functions in both neurons and immune cells.

One of the most important contributions of this study is the insight into the connection between DNA damage – a rapid consequence of memory-inducing stimuli – and the persistent cellular changes associated with long-term memory. Researchers in the same group as Jovasevic *et al.* had previously found that the gene-expression profiles of hippocampal neurons, at a remote-memory timepoint, support the formation of cellular structures called primary cilia and perineuronal nets, which are indispensable for the retrieval of remote memories[7]. In the current work, the authors demonstrated that TLR9 and RELA are each required for the formation of both structures. These results provide a molecular link between the acquisition of a memory and the ability to store it reliably for an extended period.

Despite the substantial insights provided by identification of these inflammatory neurons, pertinent questions remain. For example, which properties of memory are conferred by these neurons? And how do they interact with engram neurons? The authors speculate that inflammatory neurons could have a key role in the stability and flexibility of memories, but that engram neurons could enable the recall of memories. Perhaps the engram neurons produce the initial memory signal and the inflammatory neurons identified in this work support and sculpt the memory, enabling its persistence.

However, the activity or functional properties of these neurons during the acquisition, consolidation or retrieval of memories remain undefined. Recordings of electrical activity and selective manipulation of inflammatory neurons throughout the memory process will be needed to better understand the cells' contributions to memory persistence. Likewise, it is necessary to define the timescale over which the inflammatory response is induced following learning. Jovasevic and colleagues' analyses of gene expression in single cells represent only the first step in characterizing the molecular processes that are induced in these inflammatory neurons, and it is striking that neither *Tlr9* nor *Rela* expression was observed in this experiment.

To truly understand the nature of these neurons, it will be crucial to determine how neurons are selected to participate in either the engram or the inflammatory population. Work on engram neurons has shown that baseline expression of the transcription factor CREB, a promoter of activity-induced gene expression in memory, primes individual neurons to be recruited into the engram[8]. An analogous mechanism might exist for the inflammatory population. Could a history of DNA damage predispose certain neurons to persistent DNA damage and activation of TLR9 after learning? Previous work has outlined how somatic (non-heritable) mutations, which result from DNA damage that is accumulated during active transcription, can mark the developmental lineage of human neurons and influence their mature function[9].

Finally, the unexpected nature of these inflammatory neurons raises pressing questions, given that DNA damage plays a key part in ageing and neurodegeneration. Activation of TLR9 is also known to contribute to neurodegeneration, predominantly through microglia, the immune cells of the central nervous system[10]. How is it that, in neurons, activation of TLR9 is crucial for memory formation, whereas, in microglia, it produces neurodegeneration – the antithesis of memory? What separates detrimental DNA damage

and inflammation from that which is essential for memory? And how are these mechanisms disrupted in the context of ageing and neurodegenerative disorders? Do these mechanisms contribute to the cognitive deficits that accompany many neurodevelopmental disorders?

Much effort will be required to answer these questions. It could be that, just as Dalí used his signature surrealist style to depict both memory and its instability, the molecular mechanisms uncovered by Jovasevic *et al.* might underpin both the persistence and disintegration of memories.

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Organic chemistry

Wild beasts of the chemical landscape tamed

Kenneth F. Clark & John A. Murphy

The idea that three different free radicals could be used together to carry out specific steps in a chemical reaction has long been implausible. A 'radical sorting' strategy now achieves this feat to make organic molecules. **See p.104**

The formation of carbon–carbon bonds is at the heart of the chemistry used to synthesize pharmaceuticals, agrochemicals and advanced materials. Chemists' skills in harnessing highly reactive free radicals for this purpose have grown steadily. On page 104, Wang *et al.*[1] describe the ordered construction of molecules using reactions in which three types of radical are present simultaneously, but have distinct roles – a remarkable level of control for such highly reactive chemical species. The secret to success lies in an emerging strategy for organic chemistry, known as radical sorting.

Chemical bonds result from the pairing of two electrons. One way to form new bonds is to start with molecules, called radicals, that have an unpaired electron. Radicals form a new bond by pairing their single electron with an electron that is already paired up in another bond, thereby breaking up the other bond's pairing.

The high reactivity of radicals means that they are usually extremely short-lived and not easy to control – indeed, for many decades, controlling the chemistry of these 'wild beasts' of the chemistry landscape was viewed as a daunting task. However, over the past 50 years, the reactivities of radicals have been studied intensively, so that researchers now understand more than ever about the chemistry of these compounds[2]. The most important radicals for synthesis are those in which the unpaired electron is associated with a carbon atom. These radicals can form bonds to other carbon atoms, or to other elements, to build the organic structures of high-value materials such as pharmaceuticals.

Knowledge of the reactivities of radicals has enabled radical sorting: different radicals can be carefully chosen so that, when generated in the same reaction vessel, each one preferentially and selectively undergoes only one type of chemistry[3–8]. This has opened up opportunities for chemists to use combinations of radicals, so that each type of radical has a specific step in a reaction pathway. For example, some nickel(II) complexes undergo selective reactions with certain types of carbon radical to form carbon–nickel bonds; and the resulting nickel(III) complexes can then undergo selective reactions[9] with a different type of carbon radical to form carbon–carbon (C–C) bonds (similar reactions of radicals with bonds to metal atoms have also been reported[10–15]). Overall, this allows the selective synthesis of products.

So far, radical sorting has focused on selective reactions involving just two types of radical. Wang *et al.* now report a reaction sequence in which three types of carbon radical are generated (Fig. 1). All three are active simultaneously in the reaction mixture, and yet each one attends only to its own task. The first radical adds to an alkene (a molecule that contains a carbon–carbon double bond) to

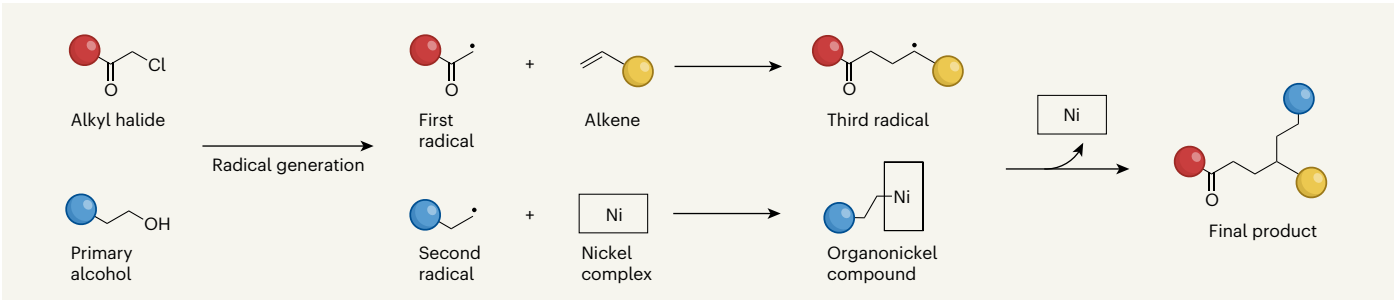

Figure 1 | Molecular construction using three radicals. Wang *et al.*[1] report a reaction in which three radicals selectively perform different tasks. The first and second radicals are generated from precursor compounds (alkyl halides and primary alcohols, respectively; dots on the radical structures indicate the characteristic unpaired electron of a radical). The third radical is formed from the reaction of the first radical with an alkene. The second radical reacts with a nickel complex, forming an organonickel compound. This reacts with the third radical, yielding the final product. The reaction pathway depends on the distinct reactivities of the radicals: the first is electrophilic and therefore reacts with the electron-rich alkene. The second and third radicals are not electrophilic. Because the second radical is not bulky, it reacts preferentially with the nickel complex. By contrast, the third radical is bulky and therefore reacts with the organonickel compound. Spheres represent any chemical group; ligand molecules in the nickel complex are represented by a rectangle.