role. Of note, there are also reported examples of SARS-CoV-2 infection generating antibodies that turn against the host. People with COVID-19 can develop antibodies that target nucleic acids[8] and host proteins[9].

It is important to remember that we do not yet know whether, in people with severe COVID-19, this antibody-mediated phenomenon is detrimental (by suppressing a natural antiviral pathway, allowing uncontrolled virus replication) or beneficial (by reducing toxic effects of a potent antiviral response). That said, these results raise the possibility that therapy to block CD32B would partially restore interferon responses in people with severe disease. However, before considering therapeutic applications, the following steps should be taken. These results need to be confirmed in a larger group of patients, the process should be examined in other types of tissue in which the virus is found (rather than just in blood samples), and a fuller explanation is needed of the mechanisms that underlie these findings.

With several anti-SARS-CoV-2 vaccines currently approved, it will be useful to determine the antibody profile that vaccination elicits, and to compare it with the profile that develops during SARS-CoV-2 infection. Such a comparison would help to reveal the checks and balances used by the immune system to help keep us alive during severe infection.

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Biochemistry

Dynamics of RNA–protein binding probed in cells

Olivia S. Rissland

An understanding of how quickly biomolecules bind and dissociate in cells is crucial for developing quantitative models of biology, but measurements of these kinetics were possible only using purified proteins *in vitro* — until now. **See p.152**

As the geneticist Theodosius Dobzhansky stated[1] in 1973, "Nothing in biology makes sense except in the light of evolution." Many modern biologists might add that nothing in molecular biology makes sense except in the light of biochemistry — without the quantitative understanding that biochemistry provides, how can biologists predict the effect of a twofold reduction in the levels of a protein during the early development of an organism, or of a tenfold increase in the concentration of another protein in cancer cells? The chasm between the streamlined experiments of biochemistry and the messy complexity of the cell has long seemed unbridgeable. Now, on page 152, Sharma *et al.*[2] report a technique that enables the biochemical analysis of molecular interactions in cells.

The authors focused on the dynamics of interactions between RNA molecules and proteins. Messenger RNA molecules are bound by various RNA-binding proteins (RBPs), which control almost every aspect of the mRNA life cycle — from the initial processing of newly made RNAs to their eventual destruction[3]. Each RBP can bind to hundreds of RNA molecules, and, in turn, each RNA can be bound by dozens of different RBPs[4]. Moreover, RNA–protein interactions are not static[5,6]. Instead, proteins can rapidly bind to their target RNAs and just as rapidly dissociate from them (Fig. 1), and these dynamics are at the core of gene regulation. In other words, the kinetics of RNA–protein interactions are a driving force of gene expression. Defining the parameters of these kinetics in cells is therefore crucial for fully understanding the regulation of gene expression.

Although RNA–protein interactions have been investigated for decades, their kinetics in cells have not been characterized. Broadly speaking, kinetic insight has been available only from *in vitro* studies using purified proteins; experiments in cells have been able to identify the RNA targets of RBPs, but lacked the precision to measure the kinetics of the interactions[5]. With the advent of high-throughput sequencing methods, *in vitro* approaches can now probe the kinetics of a protein's interactions with tens of thousands of RNA variants[7]. But these experiments are still carried out on purified proteins in the absence of the cellular milieu. In the past few years, a method called crosslinking and immunoprecipitation[8] (CLIP) has become a workhorse for the characterization of RNA–protein interactions in cells. In CLIP, a protein in complex with an RNA molecule is covalently crosslinked to the RNA using ultraviolet light; the complexes are then isolated and the crosslinked RNA is identified by high-throughput sequencing. This approach provides a catalogue of RNAs that bind to a specific RBP in the complex environment of the cell, but it provides, at best, only a snapshot of these interactions.

Sharma and colleagues now bridge the gap between *in vitro* strategies and CLIP by developing a type of CLIP that can determine the kinetic parameters of RNA–protein interactions in cells. The authors' key insight was that certain technical aspects of previously reported CLIP methods precluded such approaches from being useful for capturing kinetic parameters. The most challenging limitation is that crosslinking rates must be rapid to capture the rates at which proteins and RNA molecules associate and dissociate. Conventional UV sources cannot achieve sufficiently rapid crosslinking, and so using

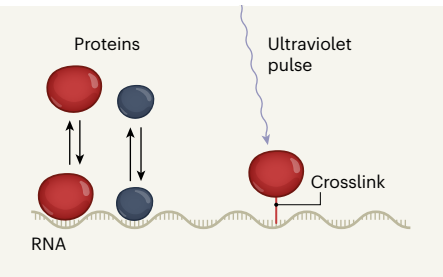

Figure 1 | A method for probing RNA–protein interactions in cells. Proteins that act on RNA molecules rapidly associate and dissociate from their target binding sites. Measurements of the rates of association and dissociation are needed for a quantitative understanding of gene regulation, but have been impossible to do in living cells. Sharma *et al.*[2] describe a method called KIN-CLIP that uses ultrafast pulses of ultraviolet light to generate covalent crosslinks between the bound proteins and RNA molecules in cells. This not only allows the RNA targets of the proteins to be identified (as was possible in previously reported crosslinking techniques), but, owing to the rapidity of the crosslinking process, also allows the kinetics of association and dissociation to be determined.

them to measure kinetics is like using a slow shutter speed to photograph a galloping horse — everything blurs together in the image. This realization led the authors to use a pulsed femtosecond UV laser, which crosslinks proteins to RNA fast enough to capture kinetic parameters. They call their method KIN-CLIP (for kinetic CLIP).

To test the method, the authors applied it to an RBP called Dazl, which is required for the production of reproductive cells, and regulates gene expression[9]. Dazl binds to hundreds of target mRNAs, increasing their stability and the number of proteins produced[10]. However, despite its biological importance, much about the binding and function of Dazl is unknown, making it an ideal candidate for KIN-CLIP experiments.

Sharma and co-workers first verified that KIN-CLIP identifies RNA targets found in previously published data sets produced from 'snapshot' CLIP. They then calculated kinetic parameters, known as rate constants, for the association and dissociation of Dazl with each of its thousands of binding sites in RNA. These results revealed that Dazl binding is highly dynamic: its binding time is short; the RBP resides at individual sites for only a few seconds. Dazl also binds rarely, and so the binding sites are free of the protein for most of the time.

The authors also found that multiple Dazl molecules tend to bind at sites that are close together. The kinetic analysis suggests that this might be due to cooperative binding — a phenomenon in which the binding of one protein to one site increases the likelihood that other proteins will bind to nearby sites. Finally, the authors incorporated the newly determined kinetic parameters of Dazl into a predictive model of its impact on gene expression, thus providing a biochemical basis for its function and setting the stage for future research.

One of the most exciting aspects of this study is the potential of KIN-CLIP for studying other RBPs, but the method does have some limitations. For instance, as with all CLIP-based techniques, the ability to crosslink the protein of interest to bound RNAs is a requirement; this can prove challenging, because some proteins do not have the necessary side chains properly oriented for crosslinking. The biggest hurdle, though, for potential KIN-CLIP converts is that specialized equipment is needed for the crosslinking: pulsed femtosecond lasers might not be easily accessible for many biologists. Furthermore, the experimental procedures and associated analysis of KIN-CLIP libraries are more complicated than are those of standard CLIP experiments, and might prove to be another barrier to adoption.

Nonetheless, this study has brought the tools of biochemistry into living cells, and, in doing so, might provide an inflection point in the study of RNA–protein interactions. The next step is to apply KIN-CLIP to other RBPs, but the prospect of bringing it to bear on other types of interacting biomolecule also glitters on the horizon. Indeed, the authors intriguingly note that pulsed femtosecond lasers can crosslink proteins to DNA — perhaps a 'DNA KIN-CLIP' is within reach. Sharma and colleagues have not just set a new standard in RNA biology, they might have also unleashed the power of biochemistry on molecular biology more generally.

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Quantum information

A step closer to optical quantum computers

Ulrik L. Andersen

A programmable photonic circuit has been developed that can execute various quantum algorithms and is potentially highly scalable. This device could pave the way for large-scale quantum computers based on photonic hardware. **See p.54**

Quantum computers promise to deliver enormous computational power and solve problems that cannot be tackled by ordinary (classical) machines. There are many hardware platforms on which quantum computing can be developed, and it is not yet clear which technology, or combination of technologies, will prove most successful. Today, the leading schemes are based on superconducting electrical circuits or trapped-ion technologies. Another approach, based on photonics, has often been considered impractical because of difficulties in generating the required quantum states, or transformations of such states, on demand. However, this method could turn out to be the dark horse of quantum computing. On page 54, Arrazola *et al.*[1] report the development of a programmable and scalable photonic circuit, and demonstrate three types of quantum algorithm on this platform.

According to quantum theory, there is an inevitable uncertainty associated with the amplitude and phase of any state of light (the phase specifies in which stage of an oscillation cycle the light wave is). If this quantum uncertainty is unequally distributed between the amplitude and phase, the state is said to be squeezed; and the more the state is squeezed, the more photons it contains. Multi-photon squeezed light is found in many quantum-optics experiments, and quantum-computing models based on these states have existed for more than two decades[2,3]. However, whether computers based on such models would be practical has been justifiably questioned, because of the quantum uncertainty.

This scepticism has disappeared in the past few years. It became clear that a relatively simple optical circuit, based solely on squeezed light, beam splitters (devices that split beams of light in two) and photon counters, could carry out a sampling algorithm (a procedure that takes a random sample of data) at a speed beyond the reach of classical computers[4]. It was also discovered that such an algorithm has many practical applications[5]. For example, it is useful in simulating transitions between states of molecules[6] and finding matching configurations of two molecules — a process known as molecular docking[7].

In the computing architecture used to implement this quantum sampling algorithm, squeezed states of light are generated and launched into an optical network consisting of several optical paths and beam splitters (Fig. 1). The squeezed states mix together when they meet in beam splitters because of a quantum effect called interference. As a result, all the states come out completely scrambled, in a way that depends on the relative lengths of the optical paths, known as their relative phases. Reprogramming these phases alters