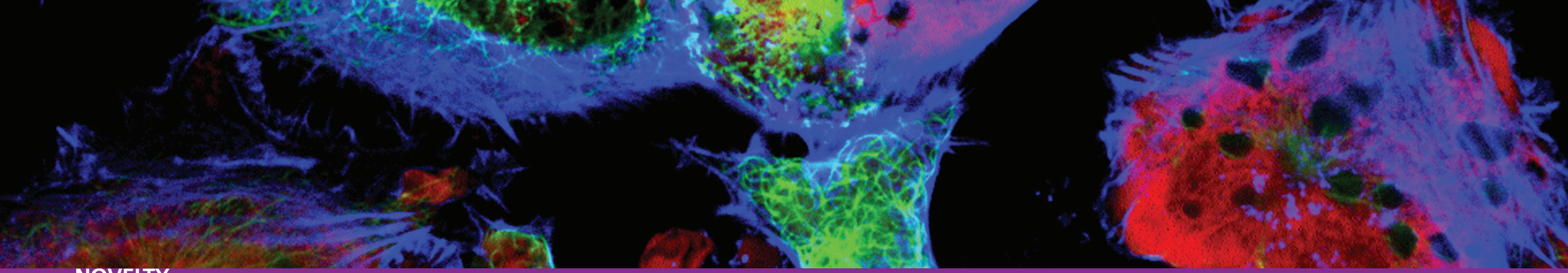

Piecing together a puzzle in protein damage

Working with colleagues in the UK and USA, researchers at the Franklin have helped solve a 20-year-old mystery surrounding an 'orphan' family of proteins called LanCLs.

As we age, and when certain pathogens attack us, marks are left on the proteins in our bodies. The international team found that key enzymes called kinases – vital to many signalling and regulatory functions within mammals – become more active rather than less active when damaged by this process. This suggests that cell signalling could be altered or disrupted by ageing or pathogen attack, adding to our understanding of this area.

The scientists also discovered through this work that LanCLs are capable of 'trapping' and removing such damaged kinases. Thanks to this research, failure to remove these damaged kinases by LanCLs is now thought to threaten the survival of the organism, as knock-out gene experiments suggest there is a high mortality in mice that do not possess these proteins.

LanCLs are found in nearly all living organisms, but their function was previously unknown.

Forming a picture

One of the most curious forms of protein damage is the creation of a carbon-carbon double bond, a process known to chemists as an 'elimination' reaction. Although some of our damaged proteins are eventually remade and replaced, some are not (or may be replaced only slowly) and may function incorrectly when damaged. For many years the consequences of this 'elimination reaction' damage and how cells respond have been unclear.

Enzymes known as LanC proteins were first identified in bacteria. Similar proteins – called LanC-like or LanCL – have since been found in many organisms and are thought to be ubiquitous within animal cells.

Researchers at the Nair lab in the Department of Biochemistry at the University of Illinois had previously solved the structure of one of these LanC-containing proteins in bacteria, noticing that the protein was bound to a kinase.

This discovery led the Illinois team to explore whether LanCL proteins could also bind to kinases, even in mammalian cells. 'We saw that they were able to bind to many kinases, including AKT and mTOR, and all of a sudden the pieces of the puzzle started forming a picture,' says Professor Wilfred van der Donk, a professor of chemistry and investigator at the Howard Hughes Medical Institute, University of Illinois.

Meanwhile, Professor Ben Davis, Next Generation Chemistry lead at the Franklin and a professor of chemistry at Oxford University, worked with Professor Graham Hutchings of the UK Catalysis Hub to show that a specific type of damage in kinases could cause them to become activated. Scientists had previously assumed that such damaged proteins would be inactive.

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>
> Professor Ben Davis

Identifying possible targets

The Franklin and Illinois researchers were subsequently able to show that LanCL performs a reaction that traps this damage by adding a small molecule called glutathione. 'We realised that when the LanCL proteins are absent, the cell has a big problem because there are active proteins floating around that need to be turned off,' says Professor van der Donk.

Professor Davis adds: 'We had been working on kinases separately to the US team and saw that when we precisely modified these proteins to explore the effect of this mode of damage, they showed some really unusual activity, becoming more active rather than less. This was also affected by then 'trapping' this damage. The news that the Illinois team had protein with apparently no function but with binding pockets that might do the same thing was one of those beautiful 'bing!' moments in science. Coming together with our collective findings, and using our shared tools in protein function to help solve this mystery, has been a wonderful – and fun – example of international collaboration. Our next steps to explore this chemistry and control this damage 'in vivo' are intriguing.'

The researchers are interested in understanding the role of these proteins and making a complete list of all the possible targets of LanCLs. 'When you have abnormal kinases, it can cause all kinds of problems, including cancer,' says Professor Jie Chen, a professor of cell and developmental biology at the University of Illinois. 'LanCL proteins eliminate these damaged kinases, and it is possible that they also affect other proteins that we are not aware of. We need to connect their cellular functions to the results we saw in the mice.'

The research, published in the journal Cell, was funded by the Howard Hughes Medical Institute, the National Institutes of Health, the Biotechnology and Biological Sciences Research Council with AstraZeneca, the Engineering and Physical Sciences Research Council via both the Franklin and the UK Catalysis Hub and also with Pfizer, the EU Horizon 2020 Programme under the Marie Sklodowska-Curie programme, and the Felix Foundation.