Obituary

Yasutomi Nishizuka (1932–2004)

Ever since the discovery of hormones at the beginning of the last century, the cellular responses to these molecules have been high on the research agenda for biologists. During the 1970s and 1980s, answers began to emerge at the molecular level, most notably through the identification of key molecules and events that follow the binding of a hormone to receptors on the cell surface, and transfer the hormonal signal to the cell nucleus to elicit a response.

So it was that terms and processes that are now textbook material were unveiled. The activation of G proteins, which are associated with hormone receptors inside the cell, leads to the activation of protein kinase A. Activated G proteins can also trigger the metabolism of phospholipids in the cell membrane, particularly cleavage of phosphatidylinositol-4,5-bisphosphate (PIP_2) into inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol, a molecule that in turn activates protein kinase C. The activated protein kinases A and C phosphorylate other proteins, initiating a cascade of phosphorylations that hand the activation signal from one protein to the next until it reaches the nucleus and stimulates the correct response.

Yasutomi Nishizuka, who died on 4 November, was one of the main figures in this biological revolution. In 1989, he was a co-winner of the Lasker award for the discovery of protein kinase C, along with Michael Berridge for the identification of IP_3 function, Alfred Gilman for the discovery of G proteins and their function, and Edwin Krebs for his pioneering work on protein phosphorylation. Gilman and Krebs later received the Nobel prize for their contributions.

Nishizuka became interested in protein phosphorylation when he visited the Rockefeller University in New York in 1964 and 1965 to work with Fritz Lipmann on how proteins are synthesized. During his stay, he purified proteins called elongation factors G and T, which aid the growth of the amino-acid chain, and elucidated the role of GTP in the process.

Nishizuka's time with Lipmann and his colleagues was comparatively brief, but it gave him a strong impetus to work on the biological function of heavily phosphorylated nuclear proteins. Lipmann had himself studied phosphorylated proteins in the 1930s, when he was a visiting scientist at the Rockefeller. But even in the 1960s, the regulatory roles of phosphate were not widely recognized, except for the conservation of bioenergy in the high-energy phosphate discovered by Lipmann, and the control of glycolysis by the phosphorylation of key proteins elucidated by Edmond Fischer and Krebs. So when Nishizuka returned to Kyoto University in 1965, he started work on an enzyme that phosphorylated other proteins, which later turned out to be protein kinase A.

Discoverer of key protein activation pathways

In January 1969, Nishizuka was appointed professor of biochemistry at Kobe University School of Medicine. His new lab had belonged to the Department of Industrial Medicine, and he was surprised to find the space occupied by bicycles and a large bathtub, with no biochemical equipment or lab benches. He wasted no time in setting up the lab, however, and attracted several brilliant medical students to join him as postgraduates. The team began studying calcium-dependent protein phosphorylation. Nishizuka originally thought that a calcium-dependent protease triggered the kinase activity in brain cell extracts, but it soon became clear that the membrane phospholipid fraction was responsible, and the activator turned out to be diacylglycerol. Nishizuka coined the name protein kinase C for this kinase, and he hypothesized that it could be linked with PIP_2 metabolism.

Nishizuka made another breakthrough in 1982, following an inspiring encounter with Monique Castagna, who visited Kobe from Paris. Castagna's interest was the tumour-promoting properties of phorbol esters, and the outcome of her collaboration with Nishizuka was the finding that these compounds activate protein kinase C continuously, thus causing uncontrolled cell growth.

Born into a medical family, Nishizuka had followed the lead of his older brother Yasuaki, a well-known pathologist, choosing to become a biochemist after studying medicine. Nishizuka began his scientific career in 1958 as the first graduate student of Osamu Hayaishi in the Department of Medical Chemistry at Kyoto University. Hayaishi had just returned to Japan from the US National Institutes of Health. At the time, Japanese biochemistry was dominated by chemistry-oriented research, mostly aimed at identifying new chemical compounds in metabolites, but Hayaishi introduced the practice of studying processes and reactions rather than just end products. Consequently, Nishizuka had a thorough grounding in enzymology, and the importance of considering the physiological function of molecules was imprinted on his science.

As a scientist, Nishizuka was very critical when considering data — I remember him as always being the last person to be convinced by new results. But he was otherwise warm-hearted and gentle, with a sense of humour. He revered the arts, particularly music (he played the piano) and painting. His artistic sense was evident in his lecture slides — quite an achievement, because for much of his career each letter had to be stencilled by hand.

On 17 January 1995, a huge earthquake struck Kobe, destroying several of the university buildings — and damaging Nishizuka's home. Only two weeks after this disaster, Nishizuka was named president of Kobe University, and in the ensuing six years of his term of office he rebuilt the university and re-established it as a competitive academic institution. At the time of his death he was serving as president of Hyogo Prefectural Centre for Adult Disease and on many government advisory committees. He will be remembered as a great and charismatic scientist.

Tasuku Honjo

Tasuku Honjo is in the Department of Medical Chemistry and Molecular Biology, Kyoto University Faculty of Medicine, Kyoto 6068501, Japan.
e-mail: honjo@mfour.med.kyoto-u.ac.jp

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