Research reveals how key controller protein is switched on

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New research has uncovered how a complex protein pivotal in the development of cancer, viral infection and autoimmune diseases is activated. The discovery answers a key question about one of the most widely-researched proteins in human biology, which has been the subject of tens of thousands of research papers and millions of pounds in research funding.

Jiazhen Zhang, a research student in Professor Sir Philip Cohen's laboratory at the University of Dundee, uncovered how the protein complex, called NF-κB, is activated. The results are published today in the *Biochemical Journal*.

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that controls transcription of DNA. NF-κB is found in almost all animal cell types and plays a key role in regulating the immune response to infection. Incorrect regulation of NF-κB has been linked to cancer, inflammatory, and autoimmune diseases, septic shock, viral infection, and improper immune development.

"NF-κB has been the subject of a vast amount of research for many years as it plays a critical role in inflammatory diseases and cancer," said Sir Philip. "It has been known for some time that the protein is activated by a kinase called IKKβ but there has been split opinion with regards to how the kinase itself is switched on.

"We have confirmed that another kinase, TAK1, is involved, but

surprisingly it isn't sufficient to switch on IKKβ. Two other events need to happen in addition, namely the formation of an unusual type of ubiquitin chain and its attachment to IKKβ and then the addition of a second phosphate group on to IKKβ which remarkably is carried out by IKKβ itself. It is only then that IKKβ becomes competent to switch on NF-κB.

"This is complex biochemistry but working out the details of how proteins are switched on and off is how new ways to develop improved drugs to treat disease are identified. For example, the enzyme that makes the ubiquitin chains needed to activate IKKβ could now be targeted to develop a drug to treat inflammatory diseases."

The research was carried out in the Medical Research Council Protein Phosphorylation and Ubiquitylation Unit (MRC-PPU) at Dundee.

Peter Shepherd, Chair of the *Biochemical Journal* Editorial Board, said, "This signalling pathway is critical for a wide range of cellular responses, particularly stress responses. Understanding how this pathway is regulated is hugely important, and this paper finally clarifies one of the key steps in this process. This is important in not only understanding the disease process, but in the quest to develop new therapies that target this signalling pathway."

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