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# Journal club

## UBIQUITIN CHAINS AS SECOND MESSENGERS

At the turn of the century it seemed that the golden era of signal transduction might be at an end. The protein kinase cascades that mediate the intracellular actions of mitogens and growth factors had been worked out, at least in outline, and no new mechanisms for transmitting the intracellular actions of extracellular signals had been identified for some years. It therefore came like a bolt from the blue when Zhijian Chen's two papers appeared, reporting that Lys63-linked ubiquitin chains were operating like 'second messengers' to transmit the intracellular actions of the cytokine interleukin-1. Similar to the way in which the other second messengers exert their effects, these ubiquitin chains interact with a regulatory subunit of an intracellular protein kinase (TAK1) to switch on its catalytic activity.

> They also connected the two research fields of protein phosphorylation and protein ubiquitylation in a most unexpected way.

Why did these two papers have such a wide impact? First, at the time they were published only the role of Lys48-linked ubiquitylation in marking proteins for proteasomal destruction was well established. The discovery of an entirely different role for ubiquitin was instrumental in focusing attention on how other ubiquitin linkages were formed and recognized by ubiquitin-binding proteins to control diverse cell functions. They also connected the two research fields of protein phosphorylation and protein ubiquitylation in a most unexpected way. Understanding how cellular processes are regulated by the interplay between these two post-translational modifications has become a fertile area of research, culminating in remarkable discoveries such as the role of phospho-ubiquitin in preventing Parkinson disease.

Zhijian Chen's papers were also beautiful examples of the power of biochemistry to dissect complex cellular processes, which inspired me to switch my own research to the regulation of the innate immune system. Like all great discoveries, the Chen papers were not the end but the beginning of a story, from which further unexpected insights have emerged in recent years.

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