Journal club

A NEW UBIQUITIN CHAIN, A NEW SIGNAL

The most surprising paper I have read in recent years was by Kazuhiro Iwai and his colleagues (Kirisako, T. *et al.*), and it has had a great impact on the work in my laboratory. Their study, published in 2006, described a novel type of ubiquitin chain in which monomers are threaded head-to-tail.

Prior to this study, ubiquitin chains were thought to be assembled only in a non-linear manner — an internal Lys residue of one ubiquitin moiety is attached to the carboxy-terminal residue of another. Iwai's group found, however, that ubiquitins can also be linked linearly, C-terminal Gly to amino-terminal Met residue.

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Moreover, the authors reported that assembly of this ubiquitin chain is carried out by two RING-type ligases (HOIL1 and HOIP) that adopt specificity for linear chains, rather than for classical ubiquitin chains, when bound together. Using elegant biochemical assays, they also showed that this unexpected new type of ubiquitin conjugation occurs *in vitro*, although its physiological relevance remained unclear.

When I first read this paper, during a flight from Osaka to Frankfurt, I had a dazzling thought: rather than functioning as a protein degradation signal, as proposed by the authors, perhaps these chains are a novel type of ubiquitin signal. After landing, however, it was business as usual and the paper was temporarily forgotten. Now, almost 3 years later, a surge of activity in my laboratory and

others has shown that this is indeed the case. Linear ubiquitylation of NEMO (Tokunaga, F. *et al.*) and the binding of NEMO (nuclear factor- κ B essential modulator) to linear ubiquitin chains (Rahighi, S. *et al.*) are important for nuclear factor- κ B activation and cellular responses to inflammatory cytokines.

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ORIGINAL RESEARCH PAPERS Kirisako, T. *et al.* A ubiquitin ligase complex assembles linear polyubiquitin chains. *EMBO J.* **25**, 4877–4887 (2006) | Tokunaga, F. *et al.* Involvement of linear polyubiquitylation of NEMO in NF- κ B activation. *Nature Cell Biol.* **11**, 123–132 (2009) | Rahighi, S. *et al.* Specific recognition of linear ubiquitin chains by NEMO is important for NF- κ B activation. *Cell* **136**, 1098–1109 (2009)