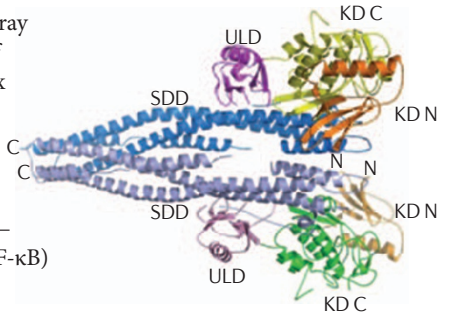
PROTEIN STRUCTURE

‘Shear’ clarity of IKKβ crystal

Reporting in *Nature*, Wu and colleagues describe the first X-ray crystal structure of inhibitor of κB kinase-β (IKKβ) in complex with an inhibitor at 3.6 Å resolution, thus revealing vital information on how this kinase — which is a target for inflammation and cancer — mediates nuclear factor-κB (NF-κB) signalling.

By using various inhibitors identified against the S177E/S181E (EE) mutant — which renders the kinase constitutively active — the authors were able to produce stable crystals of IKKβ. As crystals of a human IKKβ EE construct (residues 1–678) only diffracted to ~7.5 Å resolution, the authors instigated a search for IKKβ orthologues that could lead to improved crystals. *Xenopus laevis* IKKβ EE crystals (residues 4–675) that formed a complex with these inhibitors were able to be resolved to 3.6 Å and formed the basis of further studies.

The structure of the IKKβ dimer is described as resembling a “pair of shears”, in which the kinase domain (KD) and the ubiquitin-like domain (ULD) form the handles, and a scaffold/dimerization domain (SDD) forms the blade portion. As predicted, the inhibitors bind to the IKKβ KD at the hinge loop connecting the amino and carboxyl lobes — this region recognizes adenine in ATP. Moreover, the IKKβ KD–inhibitor complex has the typical bilobal kinase fold and the ULD has a ubiquitin fold. Interestingly, structural comparisons with other kinases showed that the SDD and ULD of IKKβ were located at similar positions to those of several known docking sites for substrates and regulatory proteins, thereby highlighting the importance of these two domains to the activity of IKKβ.



Ribbon diagram of the IKKβ dimer. Image is reprinted with permission from ‘Xu, G. *et al*’. © (2011) Macmillan Publishers Ltd. All rights reserved.

The crystal complex revealed one major surprise: the predicted leucine zipper and helix–loop–helix domains are not present as distinct structures but are part of the SDD. Indeed, most of the predicted residues in the leucine zipper motif are not available for mediating IKKβ dimerization, as they point inwards. Instead, other amino acid residues that contribute substantially to the dimerization of IKKβ — and therefore its activation — were identified. Functional experiments showed that the ULD and SDD are critical for restricting substrate specificity, whereas the ULD is required for catalytic activity.

As IKKβ mediates the activation of the canonical NF-κB pathway in response to pro-inflammatory stimuli, these data will hopefully aid the progression of numerous IKKβ inhibitors that are in preclinical development for the treatment of inflammatory diseases and cancer. Moreover, the authors propose that other members of the IKKβ family — such as IKKα and NF-κB-activating kinase — may share the same structure and function.

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ORIGINAL RESEARCH PAPER Xu, G. *et al.* Crystal structure of inhibitor of κB kinase β (IKKβ). *Nature* 20 Mar 2011 (doi:10.1038/nature09853)
FURTHER READING Baud, V. & Karin, M. Is NF-κB a good target for cancer therapy? Hopes and pitfalls. *Nature Rev. Drug Discov.* **8**, 33–40 (2009)