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Structural Insights into Inositol 1,4,5-Trisphosphate 3-Kinase B Enzyme Regulation. Philip Chamberlain¹, Mark Sandberg¹, Karsten Sauer¹, Michael Cooke¹, Scott Lesley¹, Glen Spraggon¹, ¹Genomics Inst. of the Novartis Research Foundation, 10675 John Jay Hopkins Drive, San Diego CA.

D-*myo*-inositol 1,4,5-trisphosphate 3-kinases (IP₃-3Ks) play important roles in metazoan cellular signaling. It has been demonstrated that mice without a functional version of IP₃-3K isoform B are deficient in peripheral T-cells, indicating that IP₃-3KB is essential to the developing immune system. The recent apo IP₃-3KA structure exhibited a helix at the catalytic domain N-terminus occupying the ATP binding site, with a tryptophan indole moiety mimicking the binding mode of the substrate ATP purine ring, suggesting a mechanism of autoinhibition. Here we present the structure of the complete catalytic domain of IP₃-3KB including the CaM binding domain in complex with Mg²⁺ and ATP. The crystal structure reveals a homodimeric arrangement of IP₃-3KB catalytic domains, mediated via an inter-molecular anti-parallel β -sheet formed from part of the CaM binding region. Residues from the putative autoinhibitory helix are rearranged into a loop configuration, with extensive interactions with the bound ATP. The IP₃-3KB structure suggests a mechanism of enzyme activation, and raises the possibility that an interactions between IP₃-3KB molecules may occur as part of the catalytic or regulatory cycle.