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Structure watch

AMPK GOES INTERACTIVE

AMP-activated protein kinase (AMPK) regulates metabolism by sensing changes in the AMP:ATP ratio in eukaryotic cells. The binding of AMP to AMPK and activation of its Ser/Thr protein-kinase domain have been well-characterized by previous biochemical and genetic analyses. Two studies now shed light on the structural basis for these mechanisms in mammalian AMPK and the AMPK homologue SNF1 from *Saccharomyces cerevisiae*.

Gamblin and colleagues determined the crystal structure of the mammalian AMPK regulatory fragment comprising the C-terminal domains of the α- (catalytic) and β- (regulatory) subunits and the full-length regulatory γ-subunit that contains three AMP-binding sites: two that bind either AMP or Mg.ATP and one containing a tightly bound, non-exchangeable AMP (which is not involved in AMP–ATP sensing). No significant conformational changes were observed between the AMP-bound (active) and ATP-bound (inactive) AMPK forms, so how do increased concentrations of AMP regulate AMPK activity? The authors propose that AMP binding to the two exchangeable sites allows the formation of inter-subunit interactions that cannot form when ATP is bound. This allosteric effect leads to quaternary structure changes that enhance the activity of the kinase domain and reduce its dephosphorylation rate when AMP is bound. The two exchangeable AMP–ATP sites are found on opposite faces of the disc-shaped γ-subunit in the AMPK structure, which suggests that distinct inter-subunit interactions occur that might enable separate mechanisms for allosteric activation and dephosphorylation protection by AMP binding.

Tong and colleagues also describe inter-subunit interactions in *S. cerevisiae* SNF1, a finding that confirms biochemical and genetic data indicating a direct interaction between the α- and γ-subunits that probably regulates the kinase domain. The α-subunit contains a regulatory sequence that might control both the inhibition and the activation of SNF1: inhibition could be caused by the regulatory sequence binding to the active site or interacting with a lobe of the kinase domain. Once SNF1 is activated, this inhibition is removed by sequestration of the regulatory sequence by the γ-subunit, which might represent the activated heterotrimer core of *S. cerevisiae* SNF1. The authors propose that mammalian AMPK might use a similar regulatory mechanism because the disease-causing mutation N488I in the γ-subunit of mammalian AMPK is located near the sequestered part of the regulatory sequence.

Given the role of AMPK in cellular metabolism, structural insights into the mechanisms of AMPK activation could also inform the design of AMPK-specific drugs against diseases such as diabetes and obesity.

ORIGINAL RESEARCH PAPERS Xiao, B. *et al.* Structural basis for AMP binding to mammalian AMP-activated protein kinase. *Nature* **449**, 496–500 (2007) | Amodeo, G. A. *et al.* Crystal structure of the heterotrimer core of *Saccharomyces cerevisiae* AMPK homologue SNF1. *Nature* **449**, 492–495 (2007)
FURTHER READING Hardie, D. G. AMP-activated/SNF1 protein kinases: conserved guardians of cellular energy. *Nature Rev. Mol. Cell Biol.* **8**, 774–785 (2007)