Cryo-EM structure of the agonist-bound Hsp90-XAP2-AHR complex

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Abstract

Aryl hydrocarbon receptor (AHR) is a transcription factor recognising numerous ligands including chemical pollutants, natural products and cellular metabolites, and therefore mediating a broad spectrum of physiological and malignant processes. However, the scarcity of structural data precludes a deeper understanding of the mechanisms governing its specificity and promiscuity. Here we provide a 2.85 Å cryo-EM structure of the indirubin-bound AHR complex with Hsp90 and XAP2. The structure reveals a closed conformation Hsp90 dimer with AHR threaded through its lumen and XAP2 serving as a brace. AHR forms extensive contacts with both partner proteins. Using mutagenesis, we pinpoint the residues crucial for the complex formation. We also provide a long-awaited structure of the human AHR PAS-B domain and explain the details of the interaction with its agonist. Our findings rationalise prior extensive biochemical data and provide a framework for future mechanistic studies and structure-guided drug design.