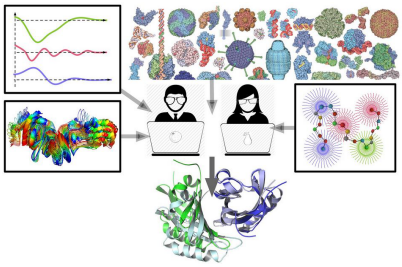

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Structural basis for the subversion of MAP kinase signalling by an intrinsically disordered parasite secreted agonist

Pathogens often evolve methods of modulating host cell signalling pathways in order to promote their growth and persistence in the infected cell. One of the most efficient methods to interact with host signalling proteins is the use of intrinsically disordered proteins combined with short linear motifs, as the evolutionary timescales involved are shorter than those required for globular domains. Short linear motifs in particular can be used to allow interactions between a pathogenic protein and that of a host in a simple manner. The causative agent of toxoplasmosis, the obligate intracellular parasite Toxoplasma gondii, has recently been shown to deliver an intrinsically disordered protein, GRA24, into the cells it infects, that directly interacts in vivo with p38α, leading to autophosphorylation and nuclear translocation of the host kinase. The molecular basis of the interaction between p38α and the linear motifs R1 and R2 of GRA24 has been determined via the crystal structure of the interacting regions of the two proteins and characterising the full complex in solution using a combinatorial approach with SAXS, EM and AFM. Through structural and biochemical data, GRA24 is shown to use the classic KIM binding mechanism to form a highly stable complex linking two kinases that promotes p38α autophophosphorylation at the activation loop creating a highly active p38α complex. Additionally, the recombinant complex forms a powerful in vitro tool to evaluate specificity and effectiveness of p38α inhibitors that have advanced to clinical trials, as it provides a hitherto unavailable stable and highly active form of p38α. This is the first structural study of pathogen intervention in a MAP kinase pathway important in the inflammatory response and may provide new lines of investigation for novel modulators of MAP kinase signalling

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