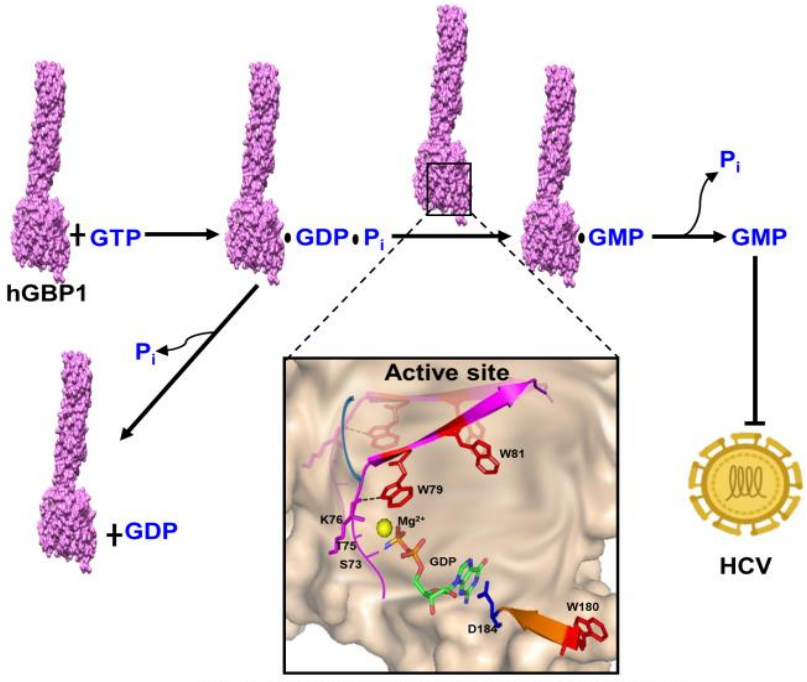
Active site repositioning in large GTPase hGBP1 during the two-step GTP hydrolysis and the effect of stimulated GMP formation on the proliferation of hepatitis C virus

Interferon inducible large GTPases are critical for innate immunity. These proteins undergo substrate-induced assembly formation, which stimulates their activity. The distinctive feature of a large GTPase, human guanylate binding protein-1 (hGBP1) is the sequential hydrolysis of GTP into GMP via GDP. Despite several structural and biochemical studies, the underlying mechanism of assembly-stimulated GMP formation by hGBP1 and its role in immunity are not fully clarified. Using combined approaches, scientists at DBT's National Institute of Immunology (NII), New Delhi, studied four tryptophan residues, located near switch regions (in and around the active site) to understand the conformational changes near these regions and also to investigate their effect on enhanced GMP formation. The W79A mutation showed significantly reduced GMP formation, whereas the W81A and W180A substitutions exhibited only a marginal defect.



Repositioning of the catalytic machinery through conformational change of W79

The W114A mutation showed a long-range effect of further enhanced GMP formation, which was mediated through W79, thereby W79 acting as a key mediator. Team also observed that

after first phosphate cleavage of GTP, the W79-containing region undergoes a conformational change, which is essential for stimulated GMP formation. Research data indicated that this conformational change helps to reposition the active site for the next cleavage step, which occurs through a stable hydrogen bonding contact between the side chain of W79 and the main chain carbonyl of K76. We also showed that stimulated GMP formation is crucial for antiviral activity against hepatitis C. Thus, the present study not only provides new insight for the stimulation of GMP formation in hGBP1, but also highlights a strategy by which the host responds to the RNA virus and controls viral proliferation. The results have been published in *the FEBS Journal*.

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