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Effect of mutations in the hydrophobic core of the E1B 55kDa on p53 and Mre11 degradation during the adenoviral replication cycle

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The adenoviral E1B 55 kDa (E1B) is a 496 residue multifunctional protein required for viral late mRNA export and for the inhibition of key cellular antiviral defenses, such as p53 and Mre11. E1B can be postranslationally modified by SUMOylation and by phosphorylation. These modifications regulate many activities of the protein and are situated near the N- and C-terminus, respectively. The tridimensional structure of the polypeptide has not been solved, but certain structural features that are important for the protein's activities have been described.The N- and C-termini also include NES and NLS sequences that are responsible for the protein's nucleocytoplasmic shuttling. Interestingly both termini seem to be intrinsically disordered. Less is known about the central region of the polypeptide. This region represents a hydrophobic core that seems to be important for the proper folding of the protein,and for its interaction with nucleic acids andproteins; however, its impact on the viral replication cycle is not clear. The E1B can assemble a Cullin-based E3 Ubiquitin ligase complex with the viral protein E4orf6 that induces degradation of various cellular substrates and seems to be required for viral late mRNA export. However, the contribution of the known protein's structural features to either of these activities is not known. In this work we have constructed adenovirus recombinants with substitutions in the hydrophobic core region of the E1B 55kDa protein, to determine its role in the viral replication cycle. Specifically, we have determined its impact on viral progeny production and its contribution in p53 and Mre11 degradation. Our results indicate that these mutations have different effects on p53 and Mre11 degradation suggesting that this region may be determinant in the protein's substrate recognition.

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