The Role of the Degron, a Protein-Degradation Motif Essential for Capsid Assembly in Adeno-Associated Virus

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Adeno-associated viruses (AAV) are popular vectors for human gene therapy, yet their more efficacious use clinically is limited by an incomplete understanding of its virion assembly. More recently, it was discovered that AAV cap gene expresses assembly-activating protein (AAP) to promote capsid assembly. However, work in our laboratory has helped establish that the capsid assembly process mediated by AAP is not maintained across all serotypes. Following capsid assembly, AAP must unbind and subsequently degrade for infectious AAV viral particles to form. My project hypothesized that the degron is located either in AAP's hydrophobic region (HR), based on the N terminal degron rule, or threonine-serine (TS) rich region, based on work by colleagues suggesting its role as a phosphodegron. This idea was further extrapolated to assess whether these two regions could have a bipartite function. To test our hypothesis, constructs were created which isolated and fused the HR or TS regions with GFP in order to assess expression by fluorescence microscopy and also protein expression by Western blots. The results demonstrate that degron location could be situated in both the HR and TS regions depending upon serotype. Initial studies cloning both the HR and TS regions could support the notion that the two regions may function together to degrade the protein. These findings provide some of the earliest evidence for the role of a degron in the capsid assembly of AAV.