

THE AMOT FAMILY OF PROTEINS BINDS AND ACTIVATES NEDD4 FAMILY LIGASES TO PROMOTE THE UBIQUITINATION OF LATS AND YAP.

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Amot adaptor proteins bind and integrate signaling that controls cell polarity and growth. All three Amot family members (Amot, AmotL1 and AmotL2) directly bind YAP; a transcriptional co-activator that controls the expression of genes involved in organ homeostasis and cell growth. Prevention of nuclear accumulation of YAP by either sequestration or degradation in the cytosol abolishes its transcriptional functions and is a major mechanism for growth arrest in response to cellular differentiation. This is mainly thought to be regulated by phosphorylation of YAP by the Hippo kinases LATS1/2. Recently, binding by the Amot proteins was also found to inhibit YAP by sequestering it in the cytosol through both LATS dependent and independent mechanisms. This study identifies a novel mechanism whereby Amot proteins control YAP activation in a Hippo independent mechanism by coupling it to ubiquitination by Nedd4 family ligases. Amot proteins mediate the coupling of Nedd4 ligases with YAP by simultaneously binding both proteins via multiple PY motifs that are recognized by WW domains in both YAP and Nedd4. Binding of Nedd4 by Amot is also shown to relieve the auto-inhibition of its ligase activity. This may be a direct consequence of binding Amot or from being re-targeted in cells by Amot proteins to endosomes. Importantly, Amot induced ubiquitination of YAP by Nedd4 proteins is shown to enhance the residence of YAP in the nucleus and in YAP activated transcription. Taken together our data suggest that Amot couples Nedd4 family ubiquitin ligases with the transcriptional co-activator YAP to drive the ubiquitination and activation of YAP.

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