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Abstract:

Murine double minute (Mdm2) is a highly modified and multi-faceted protein that is overexpressed in numerous human malignancies. It engages in many cellular activities and is essential for development since deletion of mdm2 is lethal in early stages of embryonic development. The most studied function of Mdm2 is as a negative regulator of the tumor suppressor protein p53. Mdm2 achieves this regulation by binding to p53 and inhibiting p53 transcriptional activity. Mdm2 also functions as an E3 ubiquitin ligase that signals p53 for destruction by the proteasome. Interestingly recent evidence

has shown that Mdm2 can also function as an E3 neddylating enzyme that can conjugate the ubiquitin-like molecule, nedd8, to p53. This modification results in inhibition of p53 activity, while maintaining p53 protein levels. While the signaling events that regulate Mdm2 E3 ubiquitin ligase activity have been extensively studied, what activates the neddylating activity of Mdm2 has remained elusive. My investigations have centered on understanding whether tyrosine kinase signaling could activate the neddylating activity of Mdm2. I have shown that c-Src, a non-receptor protein tyrosine kinase that is involved in a variety of cellular processes, phosphorylates Mdm2 on tyrosines 281 and 302. This phosphorylation event increases the half-life and neddylating activity of Mdm2 resulting in a neddylation dependent reduction of p53 transcriptional activity. Mdm2 also has many p53-independent cellular functions that are beginning to be linked to its role as an oncogene. There is an emerging role for Mdm2 in tumor metastasis. Metastasis is a process involving tumor cells migrating from a primary site to a distal site and is a major cause of morbidity and mortality in cancer patients. To date, the involvement of Mdm2 in breast cancer metastasis has only been correlative, with no in vivo model to definitively define a role for Mdm2. Here I have shown in vivo that Mdm2 enhances breast to lung metastasis through the up regulation of multiple angiogenic factors, including HIF-1 alpha and VEGF. Taken together my data provide novel insights into important p53-dependent and independent functions of Mdm2 that represent potential new avenues for therapeutic intervention.

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