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## Alternative splicing of MDM2 during breast tumorigenesis and mammary gland \*development

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### Abstract

The regulation of genes involved in proliferation and cell cycle control plays a critical role in normal development and differentiation. Aberrant expression of genes promoting proliferation (oncogenes) or loss of genes involved in restraining cell growth (tumor suppressors) can result in cancer. The p53 tumor suppressor protein has been demonstrated to play a critical role in both tumorigenesis and normal developmental processes. The mdm2 proto-oncogene can regulate the activity and stability of p53 protein. This suggested that mdm2 functions in development and tumorigenesis through p53-dependent mechanisms. However, mdm2 has also been shown to interact with factors involved in the regulation of cell cycle control, transcription and ribosome biosynthesis. The aim of this dissertation was to examine whether mdm2 expression during breast tumorigenesis and during normal mammary gland development in the mouse was regulated by p53-dependent or -independent mechanisms. The first segment of this work involved the analysis of alternative splicing of mdm2 mRNA during breast tumorigenesis in mice and humans. The second element of this dissertation examined the role of p53 in regulating the expression of mdm2 mRNA in adult tissues from the mouse and during normal mammary gland development in the mouse. Results from these experiments demonstrated that truncated mdm2 mRNA are expressed in mouse and human breast tissues. These truncated transcripts are predicted to code for mdm2 proteins that have lost C-terminal sequences involved in regulating proteolytic cleavage of mdm2 itself and in targeting p53 for ubiquitin mediated proteosomal degradation. ^

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