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Validating MDM2 oncogene as a cancer target

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Oncogene addition is one of the major characteristics of human malignancies. Targeting oncogene can be one of the most effective approaches to cancer therapy. We have been interested in developing oncogene inhibitors as novel cancer drug. We and others have suggested that the mdm2 oncogene be a valuable target for cancer therapy and prevention. Overexpression of mdm2 is often seen in various human cancers and correlates with high-grade, late-stage, and more treatment-resistant tumors. MDM2 is a major negative regulator of p53, the most studied tumor suppressor thus far. The MDM2-p53 auto-regulatory loop has been extensively investigated and is an attractive cancer target, which indeed has been the main focus of anti-MDM2 drug discovery. Much effort has been expended in the development of small molecule MDM2 antagonists targeting the MDM2-p53 interaction, and a few of these have advanced into clinical trials. However, MDM2 exerts its oncogenic activity through both p53-dependent and -independent mechanisms. Recently, there is an increasing interest in identifying natural MDM2 inhibitors; some of them have been shown to decrease MDM2 expression and activity in vitro and in vivo. These identified synthetic and natural MDM2 inhibitors include a plethora of diverse chemical frameworks, this presentation will focus on their biological activities in vitro and in vivo and the underlying molecular mechanisms of action, targeting MDM2 itself, regulators of MDM2, and/or the MDM2-p53 interaction. These MDM2 inhibitors can be used alone or in combination with conventional treatments, improving the prospects for cancer therapy and prevention. Their complex and unique molecular architectures may provide a stimulus for developing synthetic analogs in the future. (Supported by NIH grants R01 CA112029 and R01 CA121211 and a Susan G Komen Foundation grant BCTR0707731.)

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