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MDM2 modulates the cellular response to cdk4 inhibition

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Abstract

Cdk4 inhibitors recently earned Breakthrough Therapy Designation from the FDA and moved into phase III clinical trials in breast cancer and well-differentiated and dedifferentiated liposarcoma. Nevertheless, what determines whether patients will respond positively to CDK4 inhibitors and what might limit their effectiveness remains unclear. To address this we set out to identify the cellular and molecular basis of differential responses to PD0332991. Here we report that the post-transcriptional loss of MDM2 induced by PD0332991 can activate a p53- and Ink4a- independent senescent program. Changes in MDM2 expression after a cycle of PD0332991 treatment underlie the favorable clinical response observed in a cohort of patients enrolled in our phase II liposarcoma trial. Similar results in, breast cancer and glioma cell lines suggest that a similar pathway affects the cellular response to CDK4 inhibition, even though *MDM2* is not amplified in all of these cell types. This suggests that this novel MDM2 connection to senescence may have broad and substantial clinical implications.

Biography

Professor Koff has studied the regulation of the G1-S transition using biochemical, molecular, cellular and genetic approaches for the last 20 years, during which time he has authored more than 60 peer-reviewed reports elucidating the regulation of cdk inhibitors and the types of contributions that their loss makes to tumor development and to disorganization of normal mammalian development. He has received a number of awards and he was one of the top 250 most cited molecular biologists in the world for his pioneering work on cyclin E, cdk2 and p27. He has served on numerous review committees for the NIH and ACS and is on the editorial boards for a few journals in molecular and cell biology.