Lectures

LO8.03 POTENT INHIBITION OF HUMAN LIPOSARCOMA GROWTH AND SURVIVAL BY NOVEL MODULATORS OF THE MDM2-P53 INTERACTION

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Background: MDM2 is an important negative regulator of p53. It directly binds and inactivates p53, blocking its transcriptional activity and promoting its degradation. The MDM2 gene is amplified in > 95% of human liposarcomas, a disease for which the efficacy of systemic therapies is limited. Here, we explored the effects of SAR299155, a novel, highly potent and selective inhibitor of the MDM2-p53 interaction, on human liposarcoma cell lines and primary tumor xenografts in comparison with the classic MDM2 inhibitor Nutlin-3.

Methods: We determined MDM2 copy number, p53 mutational status, and protein expression levels of MDM2 and p53 in liposarcoma and normal cells. SAR299155 was applied to liposarcoma cells and the biological consequences were determined by immunoblot, cell viability, cell cycle, and apoptosis assays. Cells were transfected with p53 siRNA to determine the specificity of SAR299155. Nude mice implanted with primary human liposarcomas were treated with SAR299155 or vehicle. After 28 hrs, tumors were evaluated for changes in BrdU incorporation, p53, MDM2, and p21 expression, and induction of apoptosis. During and after three weeks of dosing, tumor size, animal weight and survival duration were measured.

Results: TP53 status was wildtype in 7 of 8 liposarcoma cell lines and the xenograft, all of which had genomic amplification and high-level protein expression of MDM2. Treatment with SAR299155 resulted in increased expression of p53 and its transcriptional targets MDM2 and p21. Cell viability was markedly decreased in liposarcoma cells with wild-type p53, with IC50 values of 0.4 – 1.9 µM and 2.7 – 9.8 µM for SAR299155 and Nutlin-3, respectively. These effects were abrogated by siRNA-mediated p53 knockdown and in the p53 mutant cell line. SAR299155 induced cell cycle arrest and apoptosis at about 5-fold lower concentrations than Nutlin-3. Administration of SAR299155 to mice bearing primary liposarcoma xenografts dramatically enhanced the expression of p53 and its transcriptional targets, decreased BrdU incorporation, and induced apoptosis in vivo. After 3 weeks of treatment, liposarcoma xenografts were completely and durably eliminated, and mouse survival was significantly extended.

Conclusions: SAR299155 is a specific inhibitor of the p53-MDM2 interaction with highly potent in vitro and in vivo anti-tumor activities in genetically characterized liposarcomas.