Docket #: S09-399

p53 mice - Jackson Labs stock number: 022070, 018431, 021984

Stanford investigators have found a mechanistic difference between p53's ability to induce responses to acute DNA damage (either apoptosis or cell cycle arrest) versus oncogenic stimuli. In other words, p53 variants can be active tumor suppressors but have a weak or null response to DNA damage. Compounds that inhibit p53's DNA-damage response without affecting its tumor suppression activity are desirable because p53-induced apoptosis due to DNA damaging chemotherapies and radiation therapies causes unnecessary side effects of these therapies

The researchers have developed a collection of mouse models that, in combination, can be used to screen for compounds that inactivate p53-triggered apoptosis due to DNA damage but not p53's tumor suppression activity.

In addition, the investigators have identified different gene expression signatures downstream of p53 in tumor suppression and DNA damage-induced apoptosis. These are the first known signatures to determine whether p53's tumor suppression activity is functional.

Applications

- Screening for compounds to treat cancers that do not affect p53's tumor suppression capacity but do affect its ability to respond to acute DNA damage. These compounds will protect from the severe deleterious side effects attributable to p53-dependent DNA damage responses.

Advantages

- First known functional test to determine whether p53's tumor suppression activity is functional.

- Genetically engineered mouse models and cell lines derived from these mice to screen for compounds that do not affect p53's tumor suppression and mitigate deleterious side effects of cancer therapies.

Publications

- "Distinct p53 Transcriptional Programs Dictate Acute DNA-Damage Responses and Tumor Suppression. Brady CA, Jiang D, Mello SS, Johnson TM, Jarvis LA, Kozak MM, Broz DK, Basak S, Park EJ, McLaughlin ME, Karnezis AN, Attardi LD. Cell. 2011 May 13;145(4):571-83.
- Kenzelmann Broz D, Attardi LD, "In vivo analysis of p53 tumor suppressor function using genetically engineered mouse models." Carcinogenesis, March 2, 2010.

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