Mechanisms of p53 inactivation in TP53 wild type tumors and factors affecting sensitivity to MDM2 inhibitors

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Overview

p53 is a tumor suppressor whose inactivation plays a key role in cancer development and drug resistance.
In a large fraction of tumors p53 is inactivated through TP53 gene mutations, but in some tumor types (e.g. sarcomas) p53 is inactivated despite the absence of TP53 gene mutations. In these tumors, the inactivation of p53 is often the result of increased degradation of the p53 protein mediated by the MDM2 ubiquitin ligase.

The research group led by Dr Roberta Maestro demonstrated that the overexpression of the protein Twist, detectable in a large fraction of sarcomas but also in a fraction of carcinomas, facilitates the MDM2-mediated degradation of p53 by making p53 more susceptible to MDM2 attack (1).

The p53:MDM2 interplay is the target of a number of compounds currently under clinical trials. These compounds (MDM2i) are aimed at alleviating p53 from MDM2-mediated degradation and hence at restoring the p53 tumor suppressive activity (2).

Maestro and coworkers gathered data indicating that the expression of Twist may significantly impact on the activity of these drugs.

Publications [1]**Piccinin et al., Cancer Cell, 22, 404-415, Sept 11 2012**
Other references [2]Cheok CF, Lande DP Cold Spring Harb Perspect Med. 2017 7(3).

The assay

Twist gain-of-function and loss-of-function cell models can be used
•to explore p53 inactivation mechanisms in TP53 wild type tumors
•to evaluate activity of p53:MDM2 inhibitors (MDM2i)
•to study MDM2i resistance mechanisms

What we offer
•Deep knowledge on p53 inactivation mechanisms in TP53 wild type tumors
•Solid knowhow on the generation of gain/loss-of-function cell models

What we are looking for
Partners interested in exploiting the knowhow under license or for collaborative projects

Group activity and future projects
•Identification of new biomarkers for MDM2i sensitivity/resistance
•Identification of molecules capable of restoring p53 function in p53 inhibited tumors.

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