‘WAKING UP’ SILENCED p53 IN CANCER

SUMMARY

p53 is a protein that is important for mediating cell death after DNA damage and consequently plays an important role in cancer cell death after chemotherapy. Currently, around 12 million people live with cancers containing wild-type (WT) but silenced p53. ‘Waking up’ silenced p53 represents a strategy with huge clinical potential but with significant challenges. We investigated whether in melanoma, a cancer type that retains WT p53 yet notoriously doesn’t respond to conventional chemotherapy, we could ‘wake-up’ p53 and kill cancerous cells.

We identify that cyclin B1/CDK1 phosphorylates iASPP, leading to iASPP nuclear localization and inhibition. Nuclear iASPP is enriched in melanoma metastasis and associates with poor patient survival. Most WT p53-expressing melanoma cell lines co-express high levels of phosphorylated nuclear iASPP and MDM2.

Inhibition of nuclear iASPP and MDM2 with small molecules restored p53 pro-apoptotic function. Concurrent p53 restoring and BRAFV600E inhibition achieved additive suppression in vitro and in vivo, presenting an alternative for melanoma therapy.

IASPP in the nucleus is bad news in melanoma

Why is nuclear iASPP bad news? It hijacks p53!

How does iASPP get into the nucleus and hijack p53?

IASPP: Apoptosis Stimulating Protein of p53

Rescue p53 by locking iASPP outside the nucleus and kill melanoma

References


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IASPP is a Sadisticcommander that sits in the cell nucleus. It sends out various instructions to prevent against cancer