Strategy for p53 tumour suppressor reactivation in chemo-resistant tumours

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The efficacy of current cancer treatments is often limited by the development of therapeutic resistance whose mechanisms still remain not fully elucidated. p53 is a central hub in controlling cell proliferation. To maintain genome integrity in response to cellular stress, p53 directly regulates the transcription of genes involved in cell cycle arrest, DNA repair, apoptosis and/or senescence. Mutations or alterations in the neoplastic cells of the p53 pathway adversely affect the chemotherapy-dependent cytoreduction.

We discovered that TRIM8, a member of the tripartite motif, is a p53 direct target gene that induces p53 stabilization and promotes the degradation of MDM2, directing the p53 response toward growth arrest.

We demonstrated that TRIM8 is down-regulated in clear cell Renal Cell Carcinoma (ccRCC) patients and in Colorectal Cancer (CRC) cells, impairing p53-mediated responses to chemotherapeutic drugs. RCC and CRC are not responsive to neither chemotherapy nor radiation therapy when metastases are already present and is not possible to perform surgery.

We found that TRIM8 deficit in cancer cells is due to miR-17-5p and miR-106b-5p up-regulation. Indeed, TRIM8 is a target of miR-17-5p and miR-106b-5p, whose expression is promoted by N-MYC. Reducing the levels of miR-17-5p/miR-106b-5p, we increased the chemo-sensitivity of RCC/CRC-derived cells to anti-tumor drugs used in the clinic. Intriguingly, this occurs, on one hand, by recovering the p53 tumor suppressor activity in a TRIM8-dependent fashion and, on the other hand, by promoting the transcription of miR-34a that turns off the oncogenic action of N-MYC.

p63 proteins are key transcription factors belonging to the TP53 gene family. They are involved in cell growth, proliferation, apoptosis, and differentiation, playing an essential role in epithelial stem cell biology and development. Alternative promoter usage of TP63 gene results in two main groups of proteins: the TA isoforms, which contain an N-terminal Trans Activation domain (TA) and the ΔN isoforms, which lack it.

We demonstrated that TRIM8 promotes ΔNp63α destabilization both in a Caspase 1-dependent and proteasomal ways, but only in a functional p53 background. In addition, reduction of TRIM8 cellular levels results in an increase of ΔNp63α stability, promoting a strong boost in cell proliferation and increased chemoresistance.

Taken together, our data indicate that TRIM8 simultaneously increases p53 stability and reduces the level of the pro-proliferative ΔNp63α protein, thereby playing a critical role in the cellular response to DNA damaging agents.
Reference
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