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Transcriptional regulation of cell life and death decisions by p73

AKADEMISK AVHANDLING

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Abstract

DNA is the repository of genetic information of an organism and contains the information that regulates its proper morphogenesis. Every day, our DNA is attacked by various DNA damaging agents. Our cells developed several safeguarding mechanisms, which protect DNA from different kinds of damages. Sometimes, these defence mechanisms fail and are unable to repair the DNA damage. This failure can negatively influence various biological mechanisms, *e.g.* cell cycle arrest and/or cell death, and the DNA damaged cells may thus turn into a cancer cells. Cancer cells can later become metastatic and spread to other *parts* of the body. If their spread is not controlled, they can cause serious illness and even death of an individual. Various cancer treatments aim to inhibit tumor progression by inducing cell cycle arrest and/or cell death, which are significantly mediated by the p53 family of proteins.

p73 is the second member to be identified within the p53 family and shares structure and functions with p53. *P73* generates various isoforms, which include full-length transcriptionally active (TA) isoforms and amino-terminal transactivation domain-deficient (ΔN) isoforms. TA isoforms of p73 are considered to act as tumor suppressors, whereas the ΔN isoforms of p73 act functionally analogous to other oncoproteins by counteracting the tumor suppressive functions of p53 and TAp73. In contrast to the *P53, which is frequently mutated* in a variety of human cancers, *P73* mutations are very rarely found. However, altered expression of p73 or expression of abnormal p73 splicing variants is frequently detected in different type of cancers. In some cancer cell lines overexpression of TAp73α confers resistance to anticancer chemotherapeutic agents.

In our interest to identify transcriptional activities and molecular mechanisms of p73 isoforms that influence drug-induced apoptosis, we found that TAp73α inhibits drug-induced apoptosis by inducing the expression of Hsp72, a cell survival protein, in small cell lung carcinoma cells. TAp73α can also prevent caspase-2-induced apoptosis via inhibiting its enzymatic activity. In contrast, TAp73β induces the expression of $p57^{Kip2}$, which holds tumor suppressor properties. The pro-apoptotic effects of the TAp73β isoform seem to partially depend on the induction of $p57^{Kip2}$. We discovered that different p73 isoforms transactivate cell cycle and apoptosis regulating gene promoters with different capability in a cell type-specific manner. Furthermore, we identified a functional cooperation between p53 family members, in which transcriptional activity of a DBD mutated isoform of TAp73α depends on the p53 status of the cell to transactivate cell cycle regulating *P21* gene promoter.

In conclusion, our findings help to understand the isoform-specific transcriptional activities of p73 that determines its pro- and anti-apoptotic effects, upon drug treatment. These findings are expected to help in the development of new strategies to target cancer efficiently based on the p73 isoform present in the tumour and based on the context of the cell.