“Activation of TAp73 as a strategy to combat cancer cells deprived of p53 protein”

Abstract

p53 is a transcription factor regulating a plethora of mechanisms leading to tumor suppression. Although p53 activation causes tumor regression *in vivo*, the fact that *TP53* gene is mutated in more than 50% human cancers has proven this strategy difficult to implement therapeutically. Results from cell lines and mice models demonstrate that the p53 family member, p73, can compensate for p53 tumor suppressive functions in cancers with p53 mutations and deletion. Mutations of *TP73* gene occur in less than 0.1% of all cancers, which makes p73 a promising target for cancer therapy.
Protoporphyrin IX (PpIX) was shown to induce cancer cell death by activating p53-dependent pathway. The aim of the Ph.D. project was to analyze antitumor potential of PpIX in p53-null cancers cells.

With the use of proliferation and cytometric assays together with Western blot analysis, PpIX was shown to induce intrinsic apoptotic pathway in non-small lung cancer cell line H1299 and colon cancer cell line HCT 116 *TP53* -/- . Moreover, chronic ER stress and autophagy responses were triggered by PpIX in these cell lines and contributed to PpIX-induced cell death. Protoporphyrin IX was binding to the N-terminal domain of p73 *in vitro* and stabilized tumor suppressive isoforms of p73, TAp73, in cancer cell lines and in the mouse xenograft model. TAp73 stabilization resulted from a PpIX-driven modulation of interactions with its protein regulators – Itch, MDM2 and NQO-1. The role of TAp73 isoforms in cell death induced by PpIX was prominent as knocking down *TAP73* with siRNA inhibited PpIX-induced proapoptotic *PUMA* transcription and PARP-1 cleavage.

The results of experiments performed in the Ph.D. project point to the significant role of TAp73 in stress-induced death of p53-null cancer cells. They also drive the attention to the fact that, in response to the stress stimuli, even mechanism of primarily cytoprotective function might lead to cell death. The final outcome is based on the intensity and duration of stress stimuli, activation of signaling pathways and mutual communication between processes mounted in the stressed cell.