Institutionen för Onkologi-Patologi

STUDIES ON THE MECHANISMS OF CARCINOGENESIS AND CANCER CELL DEATH

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Abstract

Gastric cancer is the second most common cause of cancer related deaths in the world. The mechanisms of gastric carcinogenesis are not fully elucidated. Telomerase and its catalytic subunit telomerase reverse transcriptase (hTERT) are aberrantly activated in gastric cancer cells and their activation disrupts a major malignant transformation barrier, namely cellular senescence and contributes to immortalization of gastric cells. In order to get further insights into the mechanisms of gastric carcinogenesis, we examined the role of two novel factors. In **study I**, the expression and function of the ATPase Reptin in gastric cancer were assessed. Reptin was up-regulated in gastric cancer samples and required for the transcription of the *hTERT* gene by cooperating with c-myc. Depletion of Reptin impaired the clonogenic potential of gastric cancer cells. In **study II,** the role of the transcription factor FoxM1 in gastric cancer was evaluated. FoxM1 was overexpressed in gastric cancer samples. Its inhibition led to cellular senescence and loss of clonogenic potential of gastric cancer cells. The induction of senescence was mediated by the $p27^{kip}$ signaling pathway. *hTERT* transcription and telomerase activity were also inhibited by FoxM1 depletion. In summary, these studies show the aberrant expression and function of Reptin and FoxM1 in gastric cancer and their potential as targets for gastric cancer therapy.

Prostate cancer is one of the most frequent malignancies and the second leading cause of cancer related deaths in men in western countries. Its development is associated with the over-activation of androgen receptor- and tyrosine kinase-dependent signaling cascades in prostate cells. One of the biggest obstacles in the clinical management of prostate cancer is the development of resistance to hormone deprivation therapy. Several tyrosine kinase inhibitors (TKI), including the multi-tyrosine kinase inhibitor sorafenib, are now in clinical trials as novel therapeutics for prostate cancer. In **study III**, we examined the mechanisms of cell death induced by sorafenib in prostate cancer cell lines. Sorafenib can induce caspase-dependent cell death in the prostate cancer cell lines, 22RV1 and PC3. Importantly, we found that different signaling cascades were targeted by sorafenib in 22RV1 and PC3 cells that may determine the cytotoxic efficacy of the drug. Furthermore, the maximal cytotoxic efficacy of this TKI was attenuated by the induction of cytoprotective autophagy in these cell lines. Combination of sorafenib with the Bcl-2 antagonist ABT737 enhanced the cytotoxic efficacy of sorafenib. Interestingly, this combination can reverse the protection mediated by primary cancer associated fibroblasts against sorafenib-induced cell death in prostate cancer cells. In **study IV,** ATG5-independent autophagy in cancer cells was described. Treatment with sorafenib can induce mitochondria depolarization and damage in these cells. The ensuing induction of autophagy restored partially the mitochondria potential but did not rescue the cells from cell death. In fact, we found that the induced autophagy was cytotoxic due to lack of expression of the autophagy key regulator ATG5. Interestingly, loss of expression of ATG5 was also observed in prostate cancer tissue samples. In summary these studies provide further insights on the mechanisms of cell death induced by the TKI sorafenib in the prostate cancer setting.

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