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p53 upregulated modulator of apoptosis and resistance to apoptosis in renal cell carcinoma - molecular mechanisms and translational implications

Fach/Einrichtung: Urologie

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Renal cell carcinoma is characterized by resistance to DNA damage-induced apoptosis leading to widespread chemo- and radioresistance. This study was designed to explore the underlying molecular mechanisms of DNA damage resistance in renal cell carcinoma in order to develop strategies to re-sensitize tumor cells to DNA damage-induced apoptosis.

Here, we found that acute DNA damage-induced apoptosis was impaired in a clear cell renal cell carcinoma line due to a disconnection between activation of p53 and upregulation of the downstream pro-apoptotic protein p53 upregulated modulator of apoptosis. Apoptosis resistance was reverted by the treatment with a histone deacetylase inhibitor, which led to a reactivation of p53 upregulated modulator of apoptosis expression. Ectopic expression of p53 upregulated modulator of apoptosis was found to re-sensitize a panel of renal cell carcinoma cell lines to four different DNA damaging agents tested. Remarkably, all renal cell carcinoma cell lines analyzed were wild-type for p53 and a knock-down was likewise able to sensitize renal cell carcinoma cells to acute genotoxic stress. Furthermore, using a tissue microarray that included matching controls for each renal cell carcinoma specimen, we made the surprising discovery that reduced cytoplasmic p53 upregulated modulator of apoptosis expression correlated with lower tumor node metastasis stage and grade as well as a favorable cancer-specific survival in compare to patients with constitutive p53 upregulated modulator of apoptosis expression.

Collectively, our results underscore the multifaceted role of p53 upregulated

modulator of apoptosis in DNA damage resistance and malignant progression in renal cell carcinoma. Impairment of p53-p53 upregulated modulator of apoptosis axis may be as a potential cause of DNA damage resistance and that reactivation of p53 upregulated modulator of apoptosis expression with histone deacetylase inhibitors could therefore be of clinical relevance. At the same time, it provide evidence that p53 upregulated modulator of apoptosis deficiency may protect from malignant progression, possibly by diminishing potentially oncogenic stimuli found to be associated with enhanced tumor cell apoptosis. Apoptosis defects as well as apoptosis-associated intratumoral changes are likely to contribute to the shaping of renal cell carcinoma genomes, which needs to be considered for the future development of novel biomarkers and therapies.