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Meeting Abstract

Novel strategies to target the survivin pathway in cancer – interference with nuclear export prevents the tumor promoting activites of survivin

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Text

Survivin functions as an apoptosis inhibitor and a regulator of cell division during development and tumorigenesis. Since survivin is a highly relevant target for tumor therapy, we investigated whether interference with it’s dynamic cellular localization represents a novel strategy to inhibit survivin’s cancer promoting functions. We confirmed survivin overexpression in head and neck as well as in colorectal cancers and identified an evolutionary conserved Crm1-dependent nuclear export signal (NES) in survivin. Importantly,

nuclear export was required for survivin mediated protection against chemo- and radiotherapy-induced apoptosis by securing efficient interference with cytoplasmic caspases. In dividing cells, the NES was required for tethering of survivin and of the survivin/Aurora-B kinase complex to the mitotic machinery, which was inevitable for proper cell division. The clinical relevance of our findings was supported by showing that preferential nuclear localization of survivin correlated with enhanced survival in a cohort of colorectal cancer patients. Targeting survivin's nuclear export by the application of NES-specific antibodies promoted its nuclear accumulation and inhibited its cytoprotective function. We here show that nuclear export is essential for the tumor promoting activities of survivin and encourage the identification of chemical inhibitors to specifically interfere with survivin's nuclear export as a novel class of anticancer therapeutics.