XIAP-associated factor 1 (XAF1), a novel target of p53, enhances p53-mediated apoptosis via a post-translational modification mechanism

117

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Background: X chromosome–linked inhibitor of apoptosis protein (XIAP)–associated factor 1 (XAF1) acts as a negative regulator of the IAP family members to mediate apoptosis. The present study aimed to determine the putative interaction and mechanism between XAF1 and p53 in human gastric and colon cancer cells, especially during process of apoptosis.

Methods: Using chromatin immunoprecipitation (CHIP) assay to investigate the interaction between p53 protein and XAF1 promoter. The XAF1 and p53 expressions were detected by reverse transcription–polymerase chain reaction (PCR) and western blot analysis. Luciferase reporter assays were used to detect activities of various promoter of XAF1 and p53 transcriptional regulation. UV exposure and adriamycin (ADR) were used to induce DNA damage on stable cell line AGS with high expression of XAF1.

Results: We first showed that XAF1 is a novel target gene of p53. Wild type but not mutant p53 was able to downregulate XAF1 at both mRNA and protein levels, which initiated from physical interaction with XAF1 promoter. In turn, over-expression of XAF1 was capable of activating p53 via post-translational modification in response to DNA damage, thereby resulting in enhancing p53 nuclear accumulation and transcriptional activity. In addition, XAF1 enhanced p53-dependent apoptosis.

Conclusions: These results suggest that XAF1 is a novel target gene of p53. Moreover, XAF1 can activate p53-mediated apoptosis via enhancing the post-translational modification of p53.

Krit1 inhibited proliferation and metastasis of human colon cancer via DPPIV signalling pathway

118

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Background: Loss of function of Krev interaction trapped-1 (Krit1) mutations contributed to cerebral cavernous malformation-1 (CCM1). Krit1 may help determine cell shape and adhesion, both crucial in angiogenesis. The aim of this study was to elucidate the potential mechanism of Krit1-midiated cell proliferation and metastasis in colon cancers.

Methods: Human colon cancer cell line HCT116 was stably transfected with full-length Krit1. Cell proliferation and invasion were measured by colony formation assay, invasion assay, and wound healing assay. Both xenograph nude mice tumour model and orthotopic nude mice tumour model were used to investigate the effects of Krit1 overexpression on tumour growth and metastasis.

Results: Overexpression of Krit1 in HCT116 cells resulted in down-regulation of colony formation ($P<0.01$) and inhibition of wound recovery and invasion. Stable expression of Krit1 significantly decreased tumour volume ($P<0.05$) and the incidence of liver metastasis in vivo. Our studies showed that overexpression of Krit1 led to restoration of dipeptidyl peptides IV (DPPIV) expression, which in association with decreased expression of downstream chemokine stromal–derived factor1 (SDF1) and its receptor CXCR4. DPPIV inhibitor Diprotin A treatment resulted in restoration of cell proliferation and migration potential in Krit1 stable expressed cells.

Conclusions: Our results showed that in colon cancer Krit1 inhibited cell proliferation and invasiveness by upregulation of DPPIV signalling pathway.