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SMAC-Survivin apoptotic “switch” is regulated through the PI3K-Src-p at the α1- Na/K-ATPase in NASH related Hepatocellular Carcinoma: studies in-vitro/vivo and in Humans.

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Introduction : Hepatocellular Carcinoma (HCC) is the second and fastest-growing cause of cancer related mortality worldwide. Our group has described the signaling properties of the α1-Na/K-ATPase (NKA) providing a pathway for organogenesis during cell development. We hypothesized that during hepatocarcinogenesis, regulation of Src-phosphorylation at the α1-subunit of the NKA causes an imbalance of the Smac/DIABLO-Survivin apoptotic signaling process, favoring cell division and tumorigenesis.

Methods : Expression of Cav-1/Smac/Survivin proteins was performed on immuno-stained HCC cell lines (Hep3 & SNU475), and livers from a NASH-HCC rodent model, and humans. Furthermore, signaling pathway studies were explored in-vitro guided by RNA sequencing. Selective blockage of Src- phosphorylation at its kinase domain was performed by administration of a synthetic peptide (33aa=pNaKtide, developed from N domain of Na/K-ATPase). Significant differences among groups were accepted at $p<0.05$ using ANOVA/t-test.

Results : α1-NKA/Src-p inhibition promoted apoptosis of cell lines, and receptor’ IC50 drove concomitantly both, Survivin's downregulation and SMAC's upregulation expressions (dose-related, $p<0.01$). In-vivo, liver tumor burden was significantly lower in animals treated with pNaKtide ($p<0.01$), and the expressions of Cav-1/Survivin were significantly higher in liver tumor tissue from non-treated when compared to treated animals ($p<0.01$). A similar pattern of Cav-1 and survivin expressions was noted in tumors from patients with NASH±HCC when compared to liver tissue from healthy subjects or subjects with liver metastases ($p<0.05$). In-vitro, Src-p at the α1-NKA activates PI3K/Akt dependent and independent to EGFr/Grb2 pathways.

Conclusions : α1-NKA/Src-p in Caveola regulates Survivin/SMAC expressions which in turn modulate a cellular “switch” from apoptosis to cell division involving two signaling pathways.

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