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Role of Na,K-ATPase in human pancreatic and liver cancer

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Na^+,K^+-ATPase is a transmembrane protein that catalyzes the active cell membrane exchange of sodium and potassium. Recent studies have suggested that, in addition to acting as an ion pump, Na^+,K^+-ATPase may also engage in the assembly of signal transduction complexes and may represent a new target in anticancer therapy. We have observed that while the expression of Na, K-ATPase's α3 subunit was elevated in human pancreatic, lung and colon cancer, the Na, K-ATPase α1 levels were increased in human hepatocellular carcinoma compared to that of normal tissues. We have found that the Na^+,K^+-ATPase α3 isoform was predominantly located near the cytoplasmic membrane in normal non-cancerous human colon and lung epithelia, however, the expression of this subunit in paired cancer epithelia was shifted to a peri-nuclear position in both a qualitative and quantitative manner. Similarly, distribution of the α3 isoform was also shifted from a cytoplasmic membrane location in spontaneously differentiated CaCO-2 cells to a peri-nuclear position in undifferentiated human colon cancer CaCO-2 cells, suggesting the distribution of Na, K-ATPase α3 subunit was regulated differently in cancer cells than in normal cells. When expression of Na, K-ATPase α3 subunits was down-regulated by knockdown of the subunit in human Panc-1 cells, the proliferation of these particular cells were reduced compared to that of control siRNA transfected cells. In contrast, no changes in cell proliferation were observed in similar cells when only α1 subunits were knocked down. Surprisingly, knocking down ATP1A1 in HCC cells markedly reduced cell proliferation *in vitro* and suppressed the tumorigenesis of MHCC97H cells *in vivo*. ATP1A1 down-regulation resulted in G1/S arrest, which was associated with a marked decrease in the level of cyclin D1 and cyclin E as well as down-regulation of AKT and STAT3. Collectively our data suggest that Na,K-ATPase subunits may be regulated differentially in different cancer types and could represent a novel therapeutic target for the treatment of malignant disease. To improve our understanding of the role of Na,K-ATPase α subunits in tumorigenesis, genetic alterations are currently being determined in control and ATP1A1 knock down HCC cells. The result of these studies will be discussed at the meeting.

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