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Inhibition of Prostate Tumor Cell Hyaluronan Synthesis Impairs Subcutaneous Growth and Vascularization in Immunocompromised Mice

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Abstract: Hyaluronan (HA), a secreted glycosaminoglycan component of extracellular matrices, is critical for cellular proliferation and motility during development. However, elevated circulating and cell-associated levels correlate with various types of cancer, including prostate. We have previously shown that aggressive PC3M-LN4 prostate tumor cells synthesize excessive HA relative to less aggressive cells, and express correspondingly higher levels of the HA biosynthetic enzymes HAS2 and HAS3. Inhibition of these enzymes by stable transfection of PC3M-LN4 cells with anti-sense HAS2 or HAS3 expression constructs diminishes HA synthesis and surface retention. In this report, we used these HA-deficient cell lines to examine the role of HA in tumorigenicity. Subcutaneous injection of SCID mice with hyaluronan synthase (HAS) antisense-transfected cells produced tumors threefold to fourfold smaller than control transfectants. Tumors from HAS antisense transfectants were histologically HA-deficient relative to controls. HA deficiency corresponded to threefold reduced cell numbers per tumor, but comparable numbers of apoptotic and proliferative cells. Percentages of apoptotic cells in cultured transfectants were identical to those of control cells, but antisense inhibition of HA synthesis effected slower growth rate of cells in culture. Quantification of blood vessel density within tumor sections revealed 70 to 80% diminished vascularity of HAS antisense tumors. Collectively, the results suggest HAS overexpression by prostate tumor cells may facilitate their growth and proliferation in a complex environment by enhancing intrinsic cell growth rates and promoting angiogenesis. Furthermore, this is the first report of a role for inhibition of HA synthesis in reducing tumor growth kinetics.

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