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Concurrent Expression of Hyaluronan Biosynthetic and Processing Enzymes Promotes Growth and Vascularization of Prostate Tumors in Mice

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Abstract: Aggressive cells in prostate cancer secrete extracellular hyaluronan (HA) as a result of up-regulated HA synthase enzymes HAS2 and HAS3. Combined detection of HA and the HA processing hyaluronidase enzyme Hyal1 in prostate tumors correlates with poor outcome. HA oligomers produced by hyaluronidases are potent angiogenic stimuli. We investigated the respective roles of HAS2 and Hyal1 using 22Rv1 human prostate tumor cells that lack both enzyme activities. Stable transfectants were selected for overexpression of Hyal1 or HAS2 and for coexpression of Hyal1 and HAS2. HAS2 overexpression elevated HA production and excess pericellular HA retention. However, HAS2-transfected tumor cell growth in culture was dramatically slowed. Coexpression of Hyal1 with HAS2 diminished HA retention but restored growth kinetics, supporting a possible combined role for excess HA synthesis and processing in maximizing unrestricted growth of prostate cancer cells. In mice, overexpression of HAS2 increased subcutaneous tumor size. Excess activity of either Hyal1 or HAS2 enhanced angiogenesis, but the most significant tumorigenic potential was realized by coexpression of both Hyal1 and HAS2 enzymes. Thus, HA production by tumor cells in prostate cancer may enhance the aggressive potential of the cells by increasing Hyal1-dependent autocrine proliferation and potentiating vascular development.

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