Tech-Trends

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In Vivo Prostate Electroporation

Function of Heparanase in Prostate Tumorigenesis: Potential for Therapy

Purpose: Heparanase is the predominant enzyme that cleaves heparan sulfate, the main polysaccharide in the extracellular matrix.Whereas the role of heparanase in sustaining the pathology of human cancer is well documented, its association with prostate carcinoma remains uncertain. Our researchwas undertaken to elucidate the significance of heparanase in prostate tumorigenesis and bone metastasis.
Experimental Design: We applied immunohistochemical analysis of tissue microarray, in vitro adhesion and invasion assays, aswell asmousemodels of intraosseous growth and spontaneous metastasis of prostate cancer, monitored by whole-body bioluminescent imaging. Electroporation- assisted administration of anti-heparanase small interfering RNA in vivo was applied as a therapeutic approach.
Results: We report a highly statistically significant ($P < 0.0001$) prevalence of heparanase overexpression in prostate carcinomas versus noncancerous tissue, as well as strong correlation between tumor grade and the extent of heparanase expression.We observed >5-fold increase in the metastatic potential of PC-3pr ostate carcinoma cells engineered to overexpress heparanase. Notably, overexpression of a secreted form of the enzyme also led to a dramatic increase in intraosseous prostate tumor growth. Local in vivo silencing of heparanase resulted in a 4-fold inhibition of prostate tumor growth, representing the first successful application of anticancer therapy based on heparanase small interfering RNA and validating the potential of heparanase as a target for prostate cancer treatment.
Conclusions: Heparanase directly contributes to prostate tumor growth in bone and its ability to metastasize to distant organs.Thus, anti-heparanase strategymay become animportantmodality in the treatment of prostate cancer patients, particularly thosewith bone metastases.

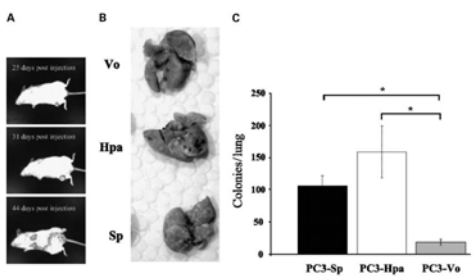

Fig. 4. Overexpression of heparanase increases pulmonary metastasis in SCIDmice. PC3-Vo, PC3-Hpa, and PC3-Sp cells, stably cotransfectedwith LUC expressing vector, were injected into the right tibia of SCID mice. A, at 46 d postinjection, when the presence of lung metastases was detected by real-time in vivo bioluminescence imaging inmice injectedwith either PC3-Hpaor PC3-Sp cells, but not PC3-Vo cells, all themicewere euthanized and their lungswere fixed and examined for the number of carcinoma colonies on the lung surface. B, gross appearance of lungs of mice injected with PC3-Vo (top), PC3-Hpa (middle), or PC3-Sp (bottom) cells. C, columns, represent the mean number of colonies per lung (n = 5mice); bars, SE. A statistically significant difference in the number of colonies per lungwas observed between PC3-Vo ^ injected and either PC3-Sp (P = 0.019) ^ injected, or PC3-Hpa (P = 0.0413)^ injected mice.

ECM® 830* In Vivo Electroporation Protocol

Tissue preparation:

Mice were anestitized and plasmid DNA was intradermally injected with 15 ug per tumor in 20uL PBS. 30-s time interval lapsed between injection and electroporation.

Electroporation Settings:

Voltage:	75V
Pulse length:	20 msec
Number of pulses:	6
Interval:	1s

Reference;

(1) Lerner, I., Baraz, L,, Pikarsky, E., Meirovitz, A., Edovitsky, E., Peretz, T., Vlodavsky, I., Elkin, M., 2008. Function of Heparanase in Prostate Tumorigenesis: Potential for Therapy. Human Cancer Biology Jan; 10.1158.1078-0432. CCR-07-1866

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