Cancer Research 2016 vol.76 N8, pages 2453-2464

Cyclin A1 and P450 aromatase promote metastatic homing and growth of stem-like prostate cancer cells in the bone marrow

Miftakhova R., Hedblom A., Semenas J., Robinson B., Simoulis A., Malm J., Rizvanov A., Heery D., Mongan N., Maitland N., Allegrucci C., Persson J.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© 2016 American Association for Cancer Research.Bone metastasis is a leading cause ofmorbidity andmortality in prostate cancer.While cancer stem-like cells have been implicated as a cell of origin for prostate cancer metastasis, the pathways that enable metastatic development at distal sites remain largely unknown. In this study, we illuminate pathways relevant to bone metastasis in this disease. We observed that cyclin A1 (CCNA1) protein expression was relatively higher in prostate cancer metastatic lesions in lymph node, lung, and bone/bone marrow. In both primary and metastatic tissues, cyclin A1 expression was also correlated with aromatase (CYP19A1), a key enzyme that directly regulates the local balance of androgens to estrogens. Cyclin A1 overexpression in the stem-like ALDHhigh subpopulation of PC3M cells, one model of prostate cancer, enabled bonemarrow integration and metastatic growth. Further, cells obtained from bone marrow metastatic lesions displayed self-renewal capability in colonyforming assays. In the bone marrow, cyclin A1 and aromatase enhanced local bonemarrow-releasing factors, including androgen receptor, estrogen andmatrixmetalloproteinase MMP9 and promoted the metastatic growth of prostate cancer cells. Moreover, ALDHhigh tumor cells expressing elevated levels of aromatase stimulated tumor/host estrogen production and acquired a growth advantage in the presence of host bone marrow cells. Overall, these findings suggest that local production of steroids and MMPs in the bone marrow may provide a suitable microenvironment for ALDHhigh prostate cancer cells to establish metastatic growths, offering new approaches to therapeutically target bone metastases. Cancer Res; 76(8); 2453-64

http://dx.doi.org/10.1158/0008-5472.CAN-15-2340