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HIV Receptor antagonists block basal breast cancer and prostate cancer metastasis *in vivo*

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Cancer is a leading cause of death worldwide and accounted for 7.6 million deaths (around 13% of all deaths. With an estimated 258 000 deaths in 2008, prostate cancer is the sixth leading cause of death from cancer in men (6.1% of the total). Breast cancer claimed more than 458,000 lives last year. In most cases the death of patients is due to metastasis. The identification of new therapeutic targets and treatments to reduce tumor metastasis requires alternative interrogation approaches and alternative strategies. We have identified a new approach through blocking the tumor metastasis "homing" process, to essentially interfere with the tumor's "GPS". Interrogation of microarray analysis of 2,254 human breast cancers demonstrated increased expression of CCL5 and its receptor CCR5, but not CCR3, in the basal and HER-2 genetic subtypes of breast cancer. Genome wide interrogation of pathways activated in patient normal breast vs. tumor identified upregulation of a CCR5 signaling module. Human breast cancer cell lines expressed CCR5 by flow cytometry and displayed a functional response to CCL5 by calcium mobilization assays and invasion assays. Using isogenic oncogene transformed breast and prostate cancer cell lines we show oncogene transformation induces CCR5 expression and that the subpopulation of cells that express functional CCR5 display increased invasiveness. CCR5 promoted metastasis homing in vivo. The CCR5 antagonists Maraviroc or Vicriviroc, developed to block CCR5 HIV co-receptor function, reduced in vitro invasion of basal breast cancer and prostate cancer cell lines without affecting cell proliferation or viability. In a series of preclinical mouse models, Maraviroc decreased breast cancer pulmonary metastasis. The isogenic prostate cancer cell lines metastasized to bones and brain in immune-competent mice representing an ideal model for testing anti-metastasis therapies. Maraviroc or Vicriviroc, reduced prostate cancer metastasis to brain, bones and lungs. Our findings provide evidence for a key role of CCL5/CCR5 in the metastasis of basal breast cancer and prostate cancer cell lines and suggest that CCR5 antagonists may be used as an adjuvant therapy to reduce the risk of metastasis in patients with the basal breast cancer subtype and prostate cancer.

Biography

Richard G Pestell received his MD from the University of Western Australia and his PhD from the University of Melbourne. He serves as the Director of the Sidney Kimmel Cancer Center and Executive Vice President at Thomas Jefferson University. He has authored ~500 peer-reviewed publications with ~38,500 citations and an H-index of 102. His papers have been published in prominent peer reviewed journals including Cell, Science, Nature Medicine, Molecular Cell and EMBO J. Dr. Pestell is funded as the Principal Investigator of three RO1 grants and Principal Investigator of the Kimmel Cancer Center CCSG grant.

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