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Kristina Shahriari
Drexel University College of Medicine, Philadelphia, USA

Prostate cancer cell cooperation enables bone metastasis

Localized prostate cancer (PCa) is fueled by androgens. The androgen receptor (AR) is also thought to play a vital role in the disseminated castration-resistant form of the disease (CRPC) that primarily affects the skeleton. Here we show that approximately 25% of PCa cells in skeletal metastases lack AR and express high levels of Interleukin-1β (IL-1β), while cells expressing AR were negative for this cytokine.

We previously identified IL-1β as a major mediator of the bone-metastatic behavior of human prostate cancer cells inoculated into the left cardiac ventricle of SCID mice. In this study, AR-/IL-1β+ human PCa cells were found to influence the bone stroma, promoting the development of carcinoma-associated fibroblasts (CAFs). Indeed, mice null for the IL-1 receptor (IL-1R) are much less prone to colonization by AR-/IL-1β+ cancer cells, as are animals treated with the IL-1R antagonist Anakinra. Thus, tumor-derived IL-1β induces the bone stroma to establish a metastasis-permissive microenvironment. Remarkably, this metastatic niche supports not only AR-/IL-1β+ cells, but also AR+/IL-1β- cancer cells that are otherwise unable to form skeletal tumors: the presence of AR-/IL-1β+ cells allowed AR+/IL-1β- cells both to colonize the bone and to persist and grow into macroscopic mixed tumors.

We propose that this cooperation among PCa cells demonstrates a functional role for phenotypic heterogeneity in human bone metastasis. These discoveries may be exploited therapeutically to alter the microenvironment of the metastatic niche, with the aim to impair establishment and progression of bone metastatic disease in patients with CRPC.

Biography

Kristina Shahriari is an M.D., Ph.D. Candidate at Drexel University College of Medicine in the final year of her Ph.D. work prior to returning to clinical training. She completed her undergraduate degree in Biology and Psychology at Carnegie Mellon University in 2007, after which she worked at the Dana-Farber Cancer Institute and Drexel University College of Medicine before beginning her doctoral studies. After completing her degrees, she plans to pursue a research residency in pathology with the ultimate goal of becoming an academic physician-scientist focused on developing highly-selective anti-metastatic agents which may be rapidly implemented in the clinic.

kss39@drexel.edu

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