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Real-time visualization of early metastasis events in Danio rerio

KANDICE TANNER, NCI/NIH

Metastasis, the process by which cancer cells travel from a primary tumor to establish lesions in distant organs, is the cause of most cancer-related deaths. One critical process during metastasis is the transit of cells from a primary tumor and through the vasculature or lymphatic systems to a distant site prior to metastatic colonization. However, visualization of cellular behavior in the vasculature is difficult in most model systems, where final cell destination is not known beforehand. Here, we used bone- and brain-tropic subclones of MDA-MB-231 breast adenocarcinoma cells (231BO and 231BR, respectively) injected into the circulation of embryonic zebrafish as a model xenograft system of metastasis. The zebrafish vasculature contains vessels on the scale of human capillaries. Real-time intravital imaging revealed metastatic spread to be an inefficient process, with less than 20% of cells passing through a given organ remaining there following 14 h of imaging. Additionally, there was no significant difference in the organ-specific residence time or migration speed of single 231BO and 231BR cells in the organ vasculature. Instead, cell capture was dependent on vessel topography and the function of integrin $\beta 1$. Interestingly, a fraction of cells extravasated from the vasculature and survived in a perivascular position in the head and caudal venous plexus for up to two weeks. In conclusion, use of the zebrafish vasculature as a model capillary bed has revealed critical steps in early metastasis that are difficult to capture in other systems.