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Invasion and metastasis: from basics to real-time imaging

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Whereas surgical resection and adjuvant therapy can cure well-confined primary tumors, metastatic disease is largely incurable because of its systemic nature and the resistance of disseminated tumor cells to existing therapeutic agents. To overcome metastatic disease, the process how tumor invasion and metastasis happen should be well understood.

Invasion and metastasis are the most insidious and life threatening aspects of cancer. Especially, lung metastasis is a serious condition of the sarcoma patients, which is difficult to treat successfully and directly affects the fate of the patients.

A cell or group of cells must be able to leave the primary tumor, invade the local host tissue, and survive at the secondary sites. This complex process requires the cells to enter into the vascular circulation, arrest at a distant vascular bed, actively extravasate into the metastatic site, and proliferate as a secondary colony. The each step of metastasis is a very complex and dynamic process during which a number of interactions between tumor cells themselves and between tumor cells and the surrounding environment take place. During the past decade, knowledge regarding the molecular and cellular processes involved in the regulation of tumor metastases has dramatically increased through the study of the migration and seeding of cancer cells, tumor–stroma interactions, vascularization of tumors, and gene expression that correlate with metastasis.

To cultivate a better understanding for tumor invasion and metastasis, we have visualized cellular behavior in primary tumors and metastatic site in vivo, using fluorescent protein expressing sarcoma cell line. For subcellular imaging, to observe cytoplasmic and nuclear dynamics in the living mouse, cancer cells were labeled in the nucleus with green fluorescent protein and with red fluorescent protein in the cytoplasm. The nuclear and cytoplasmic behavior of cancer cells in real time in blood vessels was imaged as they trafficked by various means or adhered to the vessel surface. During extravasation, real-time dual-color imaging showed that cytoplasmic processes of the cancer cells exited the vessels first, with nuclei following along the cytoplasmic projections. We also observed cancer cells seeding the lungs of live mice in real-time and follow them forming lung metastatic colonies.

Here we first summarize the current knowledge regarding tumor invasion and metastasis cascade. Then we introduce our in vivo imaging system and findings from our studies with the use of fluorescent proteins.

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