The Metastatic Cell is a Decathlon Champion

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Dr. Isaiah J. Fidler dedicated his career to the study of cancer biology and understanding the process of metastasis. He and his laboratory uncovered numerous fundamental concepts in this field and their legacy still impacts the rationale, models, and therapies for cancer today.

A cancer is defined as a malignant growth (tumor) resulting from the uncontrolled proliferation of abnormal cells. However, the cause of lethality from most cancers is not due to the primary lesion but to the growth and invasion of disseminated cancer cells in distant organs and their resistance to conventional therapies. Major obstacles to treating metastasis include the biological heterogeneity of neoplasms and the effects of the organ microenvironment. Metastasis is not random; rather, a cancer cell must endure a series of sequential, selective, and interrelated steps (likened to a decathlon) in order to result in a clinically relevant metastasis. Tumors cannot grow beyond 1-2 mm^3 without new blood vessel growth, a process called angiogenesis. Tumor-associated blood vessels are leaky and increase fluid volume and pressure in the interstitial space which induces surrounding lymphatic vessels to enlarge and sprout as well. Malignant tumor cells invade local lymphatic vessels or blood vessels and are thereby transported throughout the body. Each step in the metastatic pathway is rate-limiting and failure to complete any step prevents metastasis formation.

My laboratory and others have uncovered multiple key steps in the metastatic cascade that are regulated by Neuropilin receptors (NRP1, NRP2) including growth, adhesion, invasion, angiogenesis, and lymphangiogenesis. Recent data will be used to support the theories discovered by Fidler and the importance of understanding the "pathology of metastasis" in order to develop improved anti-cancer therapies.

Key words: cancer, malignant, metastasis, heterogeneity, orthotopic