Bidirectional Microenvironmental Cues Between Neoplastic and Stromal Metastasis Cells Drive Formation and Efficiency

Both local progression and distant metastatic spread of tumors requires a cellular interplay between neoplastic cell and the environment within which it must grow. In gliomas, the role of tumor microenvironment is critical and offers new therapeutic targets that aim to disrupt tumor biology indirectly by modulating tumor-promoting effects of the microenvironment. Similarly, as originally conceptualized by Stephen Paget in 1889, cancer spread requires both "seed" and "soil." The focus of metastasis into the brain has relied on the variable tumor biology of different tumor types from which neoplastic cells originate, as well as the genomic instability that creates survival advantages when colonizing different organs. For extra-cranial metastasis the steps of the metastatic cascade (invasion, intravasation, circulation, extravasation, and colonization) are challenging obstacles, with no one step being more restrictive than the other. In contrast, the brain poses a uniquely dynamic and challenging environment making colonization the rate limiting step. Insights into the mechanisms underlying colonization are lacking for most organ systems but most likely involve the seed, soil, and their bi-directional interplay.

Malanchi et al show that a small population of cancer stem cells is critical for metastatic colonization (Figure 1 from Nature. 2011;481(7379):85-89.), that is, the initial expansion of cancer cells at the secondary site, and that stromal niche signals are crucial to this expansion process. They found that peristin (POSTN), a component of the extracellular matrix, is expressed by fibroblasts in the normal tissue and in the stroma of the primary tumor. Infiltrating tumor cells need to induce stromal POSTN expression in the secondary target organ to initiate colonization. POSTN is required to allow cancer stem cell maintenance, required to allow cancer stem cell maintenance, and efficiency.

Figure. Cancer stem cells initiate metastasis. (A) Representative density plot showing the abundance of cancer stem cells in MMTV-PyMT breast tumours defined as CD24*CD90* after gating for viable (7-AAD−) and lin− (CD31+CD45+TER119+) cells (not shown). B, C, CSCs are the only cells to form pulmonary metastases on tail vein injection. CD24+CD90+ CSCs and non-CSC populations from GFP+ tumour cells freshly isolated from primary tumours (B; 106 cells injected each) and metastases (C; 104 cells injected each) were separately injected in recipient mice. The frequency of CSCs (red; P < 0.01 (B), P < 0.05 (C)) is maintained at the metastatic site (shown as pie charts; n = 6 each; errors, i.e.m.). Scale bar, 1 μm. D, Time course experiments show selective proliferation of CSCs during metastatic colonization. GFP+ tumour cells (106) were intravenously injected into recipient mice. At the indicated time points, the total proportion of GFP+ tumour cells in the lung (black line) and the relative amount of the CSC population (red line) were evaluated by analysis using fluorescence-activated cell sorting (FACS). Note the transient increase of CSCs after one week (n = 4 per time point; errors, i.e.m.). E, F, CSCs are the only cells able to initiate growth in a short-term in vivo colonization assay. E, One week after tail vein injection of 106 GFP+ tumour cells, mice were injected with BrdU. After 2 hours, CSC and non-CSC were isolated by FACS and the frequency of proliferating cells was evaluated by BrdU staining on cytospins (n = 12; P < 0.05; errors, i.d.; representative example is shown on the right). Note the increase of proliferation in the CSC population during the early phase of lung colonization; by contrast, proliferation does not significantly differ between the two populations in the primary tumour. F, GFP+ CSCs (2 × 106) or GFP+ non-CSCs (4 × 106) were tail vein injected and analysed after two weeks. CD90+ (CD24−) depleted non-CSC remained as single cells whereas CSCs were able to initiate growth and form metastases of different sizes (S, 30–300 cells; M, 300–3,000 cells; L, >3,000 cells). The upper panel shows a representative example of the different metastasis colonies and the results are cumulatively quantified in the bottom panel (n = 6). Scale bars, 20 μm (E) and 250 μm (F). (Reprinted by permission from Macmillan Publishers Ltd: Nature. Malanchi I, Santamaria-Martinez, Susanto E, et al. Interactions between cancer stem cells and their niche govern metastatic colonization. 2011;481(7379):85-89.)
and blocking its function prevents metastasis. POSTN recruits Wnt ligands and thereby increases Wnt signaling in cancer stem cells. We suggest that the education of stromal cells by infiltrating tumor cells is an important step in metastatic colonization and that preventing de novo niche formation may be a novel strategy for the treatment of metastatic disease.

The data describe novel insights both into the “seed” and the “soil.” Cancer stem cells or tumor initiating cells are required for the original colonization of the target organ, and their exclusion from xenografted cells leads to decreased metastatic efficiency. Interestingly, after the cells of arrive at the target organ, they proliferate during the initial growth phase of the tumor and are responsible for cellular expansion. During this period they exhibit a greater than usual fraction of the tumor, functioning to fuel tumor expansion. From the perspective of the “soil,” these metastatic cancer stem cells induce expression of stromal proteins that facilitate colonization by making the target organ’s molecular and cellular ecosystem more inhabitable. The scientific insights presented in this article could most intriguingly be applied to the brain microenvironment in the context of brain metastasis. Neuroscience remains in its relative infancy and with its further elucidation opportunities will arise to treat brain tumors not only by targeting the tumor itself, but also by exploiting the most complicated biological milieu within which they grow—the brain.

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A Novel Target for Ischemic Stroke Therapy: Pannexins

Targeted therapies to limit the death of brain tissue in ischemic stroke remain an intense area of research. The current armamentarium of the neurologist and neurointerventionalists is limited to tissue plasminogen activator (tPA) and mechanical thrombolysis. Although these therapies strike at the root cause of ischemic stroke, they offer little in the way of true neuroprotection. Neuroprotective agents in ischemic stroke and other diseases are a holy grail—their efficacy and relative safety are the holy grail. Those still seated are forming integrated health systems in which hospitals, insurers, physicians, employers, and patients align to meet healthcare needs through collaboration, shared risk and a focus on reigning in costs while insuring higher quality. Neurosurgeons need to pay attention to the trends or risk losing their position in the newly developing healthcare arena.

In a thought-provoking article in The Wall Street Journal, “The Future of U.S. Health Care: What Is a Hospital? An Insurer? Even a Doctor? All the Lines in the Industry are Starting to Blur,” writer Anna Wilde Mathews describes these changes and how they are playing out among stakeholders.1

The author explains that hospitals in many cases are merging into large systems, building vast physician networks and excluding insurance middlemen from negotiations with employers.