SERPINs shelter the endowed migrants in a hostile land

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Since metastatic lesions of solid tumors are the major cause of mortality in cancer patients, understanding the molecular mechanisms of metastasis is of paramount importance. Although extensive knowledge has been accumulated regarding the early steps in metastasis—starting with the departure of cancer cells from their primary sites, to their transit through the hematogenous and/or lymphatic systems, and ending with their entrance into the parenchyma of distant organs—it is difficult if not impossible to translate such knowledge into medicine due to the challenge of identifying patients with only primary tumors but otherwise pristine organs. In other words, autopsy studies indicate that a large proportion of patients already harbor dormant, undetectable micrometastases at the time of cancer diagnosis (Hensel et al., 2013). Accordingly, stopping tumor cell dissemination is too late for these patients. Therefore, understanding the survival and outgrowth of micrometastases may hold greater promise to combat metastatic disease.

See also: M Valiente et al (February 2014)

The classic depiction of metastatic outgrowth implies a passive selection, indicating that when the emigrated cells land on a new “soil” that produce the same growth factors akin to their primary site, they will take root and thrive at the appropriate site. Recent studies reveal a more active role played by the metastasized tumor cells, in which they modify the new host tissue to endow characteristics similar to their homeland (Valastyan & Weinberg, 2011; Malanchi et al., 2012). Both scenarios suggest that the host tissues play an accommodating role. In the recent issue of Cell, Valiente et al (2014) discovered a novel function of the brain in actively resisting metastatic outgrowth and uncovered a fascinating molecular interplay between the micrometastases and the host organ that renders a selected subset of cancer cells the ability to settle and flourish in a hostile environment.

Utilizing the in vivo selection system developed in the Massagué laboratory, Valiente et al isolated and profiled multiple lung and breast cancer cell lines capable of forming brain metastases. They discovered that four SERPINs (I1, B2, E2, and D1), either individually or in combination, are up-regulated in six brain metastatic sublines relative to their parental cell lines or their sibling bone metastatic sublines. Since these SERPINs are capable of inhibiting plasminogen activator (PA), they went on to investigate the role of PA and its product plasmin in brain metastatic outgrowth. They found that the invading tumor cells activate the nearby astrocytes, a reactive cell type in the brain, to produce urokinase and tissue plasminogen activators. The PAs then cleave plasminogen to generate plasmin, which exerts dual inhibitory actions on the invading cancer cells: it cleaves astrocyte-derived Fas ligand (FasL) to produce soluble FasL (sFasL) that can now diffuse to induce apoptosis in cancer cells at a distance; it also inactivates LICAM expressed by the metastatic cells and brain endothelial cells, thereby preventing cancer cells from spreading along the brain capillaries and coalescing among themselves, which appears to be a prerequisite for cancer cell proliferation and the subsequent formation of macrometastases. Under the strong host-derived negative selective pressure, a preexisting subset of cells with elevated levels of the aforementioned SERPINs counter the inhibitory activity of plasmin as these SERPINs inhibit PA activity, reduce brain-derived plasmin levels, shield the invading cells from the killing action of sFasL, and allow them to take up a perivascular niche that permits spreading and proliferation. This study uncovers a new level of intricate interplay between invading cells and the host organ, where both parties play active roles (Fig 1).

Like many good studies, the findings by Valiente et al raise many important questions. Here are several examples. Since the brain is an organ with low metastatic frequency (Disibio & French, 2008), is the active anti-metastasis activity identified in this study unique to the brain? Do invading tumor cells frequently trigger defensive responses by resident reactive cell types in new host organs? If so, is the mechanism shared or idiosyncratic in each organ? Why do invading tumor cells have to coalesce and spread along capillaries in order to proliferate in the brain, and what are the molecular mediators of the enhanced proliferation? Is perivascular spreading a common feature in human brain metastases?

It is clearly desirable to turn exciting discoveries like this into medicine. The first step in translating the current finding into preventing/treating brain metastatic outgrowth is further validation of the correlative data in cancer patients. It is encouraging that other groups have also identified elevated PA inhibitor expression in human
primary and metastatic brain tumors (Rao et al., 1993) and that the authors reported a correlation between SERPINI1/SERPINB2 expression and the incidence of brain relapse in 106 lung cancer patients. However, such a correlation did not hold up in breast cancer patients, presumably owing to a more complex natural history of breast cancer as the authors proposed. Furthermore, as the positive results are from small-scale discovery studies, the validity of these data depends on their replication in a much larger cohort of patients using analyses that incorporate other covariates including tumor staging, histologic and molecular subtypes, precise anatomical location at the primary sites, and treatment history.

Since SERPINs are secreted factors with known biochemical activities, they constitute druggable targets. In addition, as the events discussed in this study are late steps in the metastatic process, they are amenable to therapeutic intervention in patients who already harbor dormant micrometastases. If the mechanism uncovered by Valiente et al. is indeed relevant to human disease, it could open a realistic opportunity to develop therapeutic strategies for the treatment of brain metastases. Furthermore, if the principles learned in this study are generalizable beyond metastatic colonization in the brain, then we are one step closer to targeting metastases in multiple organs.

**Conflict of interest**
The author declares that she has no conflict of interest.

**References**


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**Figure 1.** Panel A: When tumor cells invade the brain parenchyma, they activate nearby astrocytes to produce PA. PA cleaves plasminogen to generate plasmin. Plasmin not only cleaves FasL to produce sFasL, which triggers tumor cell apoptosis at a distance, but also inactivates L1CAM to prevent tumor cells from spreading on capillaries and coalesce among themselves, which hinders tumor cell proliferation. The dual activities of plasmin effectively restrict the outgrowth of metastasized cancer cells. Panel B: A small subset of cancer cells express elevated levels of SERPINs, which inhibit PA activity to reduce brain plasmin. This action counters the dual suppressive function of plasmin and not only allows the SERPINHIGH cells to escape killing by sFasL, but also enables them to spread along capillaries and to coalesce among themselves, thus leading to aggressive proliferation and ultimate colonization in the brain.