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GENETICS

Serpins' role in brain metastasis uncovered

Little is known about brain metastasis, despite the fact it is the most common neurological complication of cancer. Most cancer cells that leave primary tumours do not survive, but an unknown mechanism allows the few cells that do survive to thrive in the brain. Joan Massagué and coauthors had already established mouse models of lung and breast cancer—the main sources of brain metastasis—and decided to "search for shared molecular mechanisms for metastasis initiation in the brain that would be common to the two very distinct types of cancer," explains Massagué.

The researchers hypothesized that the brain microenvironment must be imposing the same selective pressure on the cancer cells that infiltrate this organ. They studied brain metastasis-associated gene signatures from breast and lung cancers to identify shared genes that were concordantly deregulated in multiple experimental models of these two diseases. The key questions they asked were: "What kills most of these cells on arrival in the brain? What saves the few survivors? What allows these survivors to seek a supportive niche?"

The authors showed that many cancer cells that enter the brain are killed by reactive astrocytes, which secrete the lethal cytokine Fas ligand (FasL) and the protease plasmin that releases membrane-bound FasL into the microenvironment. "We also found that metastatic cells can survive by overexpressing neuroserpin and other members of the serpin family that prevent the accumulation of plasmin in the brain," explains Massagué. The surviving cancer cells additionally co-opt brain capillaries by adhering and hugging the vessels by means of the cell-adhesion molecule L1CAM. Cancer cells then proliferate to form a sheath around the capillaries, where they remain protected and develop into a full-blown tumour.

Massagué highlights the implications of these findings, "we see no reason that vascular co-option and the role of L1CAM should be specific to brain metastasis. Therapeutic intervention at the level of FasL, plasmin or serpins is probably out of the question. However, targeting vascular co-option is not. If this is a general phenomenon in tumour progression, the implications would be huge."

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