Metastasizing Cancer Cells Face Harsh Conditions

BY DAMIAN McNAMARA
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TORONTO — "Survival of the fittest" might be the best way to explain the genetic and molecular machinery behind cancer metastasis.

Researchers believe that overexpression of some genes in melanoma and other cancers allows some cells to survive the very harsh conditions that occur as they leave a primary tumor, travel to a distant site, and establish a new location for malignancy. "It is a similar theme to Darwin with natural selection, although it works out in a microenvironment," Dr. Youwen Zhou said.

"Why do I think this is a big deal? We still do not have a cure for metastatic melanoma, and next year another 900 or so patients [in Canada] will die from melanoma," Dr. Zhou said.

Melanoma was the sixth most common solid cancer for men in Canada in 2005 and 2006. There were 3,900 new cases last year. Of 840 deaths in 2006 from melanoma, 90% involved metastatic disease, said Dr. Zhou, who is on the faculty in the department of dermatology and skin science at the University of British Columbia, Vancouver.

There are some reasons for optimism, however. Understanding the molecular machinery might permit earlier intervention through better diagnostic or prognostic tools, Dr. Zhou said at the annual conference of the Canadian Dermatology Association.

Serum protein testing, for example, might lead to more accurate estimates of prognosis. The melanoma-inhibiting activity (MIA) protein is detected in high amounts in 100% of patients with metastatic melanoma so far. "About 20% of patients with primary melanoma will have signs of this protein in their serum. If they are negative for MIA protein, not one of them developed metastasis over time," he said.

Genetic insights also may lead to new therapeutic targets. "Selective gene silencing may work to cause metastatic cells to die," Dr. Zhou said.

So how do invasive tumors develop? Metastasis occurs when genetically unstable cancer cells adapt to a tissue microenvironment distant from the primary tumor (Cell 2006;127:679-95).

Other investigators have identified individual genes that are amplified in metastatic melanoma (Cell 2006; 125:1269-81).

The vast majority of the most aberrantly upregulated genes are able to work in concert to modify the microenvironment to their advantage.

A high degree of heterogeneity in melanoma tumor cells may in part explain why aggressive gene clones arise.

"If you look at a melanoma clinically, it has signs of molecular and cellular heterogeneity, for example, irregular borders. On a cellular level, pathologists use variation in cell size as a diagnostic factor," he said.

Dominant genetic clones can cause a higher resistance to apoptosis, greater tolerance to hypoxia and nutrient deprivation, altered cell adherence, and increased genomic instability.

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Before these breakaway cells become "little tumor thrombi," they must break through local physical barriers, he explained. They do this in part by degrading the collagen matrix. Then they have to overcome the vascular wall and survive the harsh sheering and other forces of the vasculature.

Some will survive intravasation with the right molecular defense mechanisms. Extravasation occurs when they arrive at a destination, change adhesion properties, and again pass through the vascular wall. Finally, the cells must continue to defend themselves against host defenses for distant colonization to be successful, Dr. Zhou said.

Development of novel targeting strategies against this genetic and molecular machinery is needed, he said. Once those strategies are identified, the next step would be large scale trials to assess these therapeutic targets. ■