

Rethinking Tumorigenesis in Melanoma and Other Cancers

Recent findings question a current theory of tumorigenesis, suggesting new avenues for research and therapeutic development.

Therapeutic strategies in oncology emphasize eradication of tumors and prevention of recurrence or metastasis. To this end, research and therapeutic development recently have focused on understanding mechanisms of tumorigenesis and metastasis. A current theory implicates cancer stem cells in initiating cancer growth and promoting recurrence and development of drug resistance. While there is some compelling evidence for this theory, detractors point out potential flaws in the supporting research. In the case of melanoma, a recent investigation¹ has led to greater questioning of the cancer stem cell model.

The Stem Cell Model in Brief

Cancer stem cells (CSC), according to Vezzoni and Parmiani, “can be operationally defined as a subset of neoplastic cells which are responsible for the growth and re-growth of primary and metastatic tumors.”² Likening CSCs to do-it-all action-movie star Bruce Willis, Fabian et al explain that, “through asymmetric division, CSCs supposedly drive tumor growth and evade therapy with the help of traits shared with normal stem cells such as quiescence, self-renewal ability, and multidrug resistance pump activity.”³

CSCs or cells with CSC properties have been identified in various solid tumor cancers, including breast,⁴ brain,⁵ liver,⁶ and pancreas.⁷ Such cells have also been identified in melanoma. Nguyen et al cultured

metastatic melanomas in growth medium suitable for human embryonic stem cells absent a suitable matrix and found that in 20 percent of cultures, a subpopulation of cells propagated as nonadherent spheres⁸—a

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known characteristic of stem cells. When suitable matrices that encourage differentiation of stem cells were provided, individual cells from melanoma spheres were found to differentiate “into multiple cell lineages.” The team concluded “that melanomas can contain a subpopulation of stem cells that contribute to heterogeneity and tumorigenesis.”

Earlier last year, Schatton et al reported that they had observed a sub-population of human malignant-melanoma-initiating cells (MMIC) that were identifiable by their expression of the chemoresistance mediator ABCB5.⁹ Human-to-mouse xenographic transplantation revealed that ABCCB5+ cells had greater tumorigenic capacity than ABCCB5- cells. To assess the role of ABCB5+ cells on growth of established tumors, the researchers systemically administered a monoclonal antibody cytotoxic to ABCB5+ MMIC. Administration exerted tumour-inhibitory effects.⁹

Challenging the CSC Model

Despite the accumulated evidence, there is no consensus regarding the accuracy of the CSC model for cancer, and the older clonal evolution model persists. Although they admit, “the CSC hypothesis could be of clinical relevance, especially in the definition of new ways to assay drug sensitivity of primary human tumors,” Vezzoni and Parmiani note that it remains unclear, “whether the ‘transformed’ cell is the neoplastic counterpart of a normal stem cell or whether complete malignant behaviour can occur in a more differentiated cell.”²

This summer, researchers demonstrated shortcomings inherent in the existing research on CSCs. Yoo and Hatfield note that the available evidence for CSCs derives from studies of specific suspicious cells xenotransplanted in immunocompromised

mice.¹⁰ They chose, instead, to perform allografts of cells derived from randomly-selected single cells in mouse breast and lung cancer lines. All allografted cells formed tumors.

A study published last month questions the role of CSCs in cutaneous melanoma and further challenges the existing research on CSCs.¹¹ Studies to this point have investigated the activity of CSCs xenografted to non-obese diabetic/severe combined immunodeficiency (NOD/SCID) mice.

Quintana et al investigated the effects of modified xenotransplantation assay conditions, “including the use of more highly immunocompromised NOD/SCID interleukin-2 receptor gamma chain null (Il2rg -/-) mice.”

About 25 percent of unselected melanoma cells—from both primary and metastatic melanomas—from 12 patients formed tumors in these mice. For single-cell transplants, 27 percent of unselected melanoma cells from four patients formed tumors.

Findings do not disprove the cancer stem cell model, according to the researchers, but it raises important questions. In a report on the Howard Hughes Medical Institute website (www.hhmi.org/news/morrison20081204.html), study investigator Sean J. Morrison says that cancer stem cells may play a more significant role in certain cancers compared to others and suggests only a minor role in melanoma. “As is often the case, the truth is probably somewhere in between the two prevailing theories,” Morrison stated. He added, “Many cancers will be like melanoma, a good old-fashioned cancer in which every cell is bad.”

Bad Cells

Findings from the recent study would seem to suggest that roughly one in four melanoma cells is capable of pro-

moting tumor growth or metastasis. Those are good odds for cancer but unfavorable ones for patients. Research into CSCs will no doubt continue generally, and while a direct application to melanoma treatment now appears less likely, continued investigation may yet yield important new insights into detection, management, and prognostic calculation in melanoma.

Although CSCs do not seem to represent an important therapeutic target in melanoma, researchers will continue their quest for appropriate targets and related therapies. ■

Dr. Wolfe has no relevant disclosures.

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NEW In Your Practice

A New Hope. There may be a promising new drug in the pipeline for melanoma, according to a recent report (*J Clin Oncol* 26: 5950-5956.). In an early-stage trial involving patients with melanoma that had metastasized to other sites in the body, the biological drug ipilimumab was generally well tolerated and showed signs of attacking the malignancy, researchers reported. The study involved 88 patients with unresectable metastatic melanoma who were given either a single high dose of ipilimumab, multiple low doses, or multiple medium doses. Researchers observed durable response in all groups, and concluded that the multiple medium-dose regimen provided the best result.

Wash Away Cellulite. For women looking to minimize the appearance of cellulite, Glytone's Lipo-Lift Massage Kit might deliver what they desire. The two-piece kit was designed to visibly reduce the appearance of dimpled skin by combining a cleansing gel with key firming ingredients including glycolic acid with a massaging device for manual stimulation of microcirculation, intended to smooth the skin and promote the elimination of toxins, the company says.

Also available through Glytone is a step-up system for those concerned with cosmetic signs of aging. The system provides a customized “step-up” approach using increased levels of free glycolic acid in a facial cream, facial lotion, and exfoliating lotion. Patients can “step-up” to higher levels of glycolic acid along the way from 10 percent, to 15 percent, to 20 percent.