Melanoma Stem Cells May Hold Treatment Key

BY BARBARA J. RUTLEDGE
Contributing Writer

BUENOS AIRES — The successful treatment of melanoma in the future is likely to be a two-step process involving combination therapy, Meenhard Herlyn, D.Sc., said in a keynote address at the 21st World Congress of Dermatology.

The aim of the initial treatment will be to debulk the tumor from the major transit-amplifying cells. The second stage will then be to focus on eradication of the cancer stem cells.

"If you do not eliminate these tumor stem cells with therapy, the tumor will come back over and over again," said Dr. Herlyn, professor and program leader in the molecular and cellular oncogenesis program at the Wistar Institute, Philadelphia.

Melanoma arises from malignant transformation of melanocytes or nevus cells, which are formed by overproliferation of melanocytes. Progression from nevi occurs in approximately 50% of melanomas. In normal skin, keratinocytes control the growth of melanocytes in a sort of master-slave relationship.

The decoupling of melanocytes from keratinocytes is the first step in the development of nevi. Overproduction of growth factors from fibroblasts then drives melanocyte proliferation, Dr. Herlyn explained.

For development of melanoma, the most important pathway is the mitogen-activated protein (MAP) kinase pathway, he said.

A genomewide screen performed at the Wellcome Trust Sanger Institute showed that approximately two-thirds of melanomas harbor an activating mutation in BRAF, one of the Raf isoforms in the MAP kinase pathway (Nature 2002;417:949-54).

In 98% of these cases, the BRAF mutation is V600E. A single mutation, however, is not sufficient for the development of melanoma.

Mutations in other signaling pathways, such as the P13-kinase/Akt pathways or cell cycle regulatory pathways, have also been implicated in the development of melanoma, said Dr. Herlyn, who reported no conflicts of interest.

Earlier models of cancer development assumed that melanoma arose as the accumulation of sequential mutations in a mature, differentiated melanocyte eventually leading to malignant transformation of the cell. Identification of another type of cell in melanomas, however, suggests that this model may be too simplistic.

"There are rare cells in tumors that act like stem cells and always replenish the tumor with new cells," said Dr. Herlyn.

The cell that undergoes malignant transformation to produce melanoma might not be a terminally differentiated cell, but instead might be a type of stem cell.

When they are grown under conditions suitable for embryonic stem cells, melanoma cells form spheres that look similar to embryoid bodies formed by human stem cells (Cancer Res. 2005;65:9328-37).

These melanoma spheres meet the definition of tumor stem cells. Melanoma spheres are capable of self-renewal. The cells are highly tumorigenic and quickly form lethal melanomas when injected into nude mice.

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DR. HERLYN

They also are multipotent—under laboratory conditions, melanoma spheres can differentiate into melanocytes, adipocytes, chondrocytes, and osteoblasts.

"There is an incredible plasticity in melanoma cells that we have not known before," said Dr. Herlyn. "The question is: What is the true melanoma stem cell?"

Melanoma spheres consist of a mixed cell population. Among the population are cells expressing the hematopoietic marker CD20 and cells expressing the embryonic stem cell marker CD133. Melanoma spheres include side population cells that extrude Hoechst dye via active efflux.

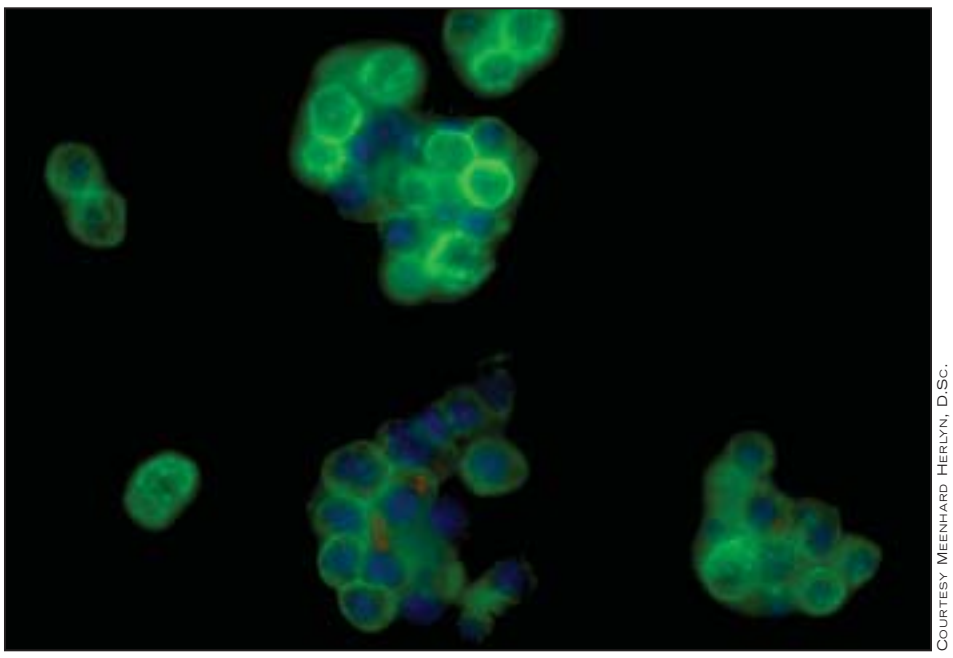
Particularly intriguing are the label-retaining melanoma cells, which proliferate slowly or not at all. When removed from the surrounding cells, however, the label-retaining cells begin to divide rapidly. "If you isolate them, they literally explode," he said.

The label-retaining cells may be the melanoma stem cells, responsible for tumor dormancy and relapse. In this model, the CD20 cells, the CD133 cells, and the side population cells function as progenitor cells.

The label-retaining cells and the progenitor cells could give rise to transit-amplifying cells, Dr. Herlyn suggested at the meeting.

Melanomas are phenotypically heterogeneous tumors. "Tumor heterogeneity is not random," he noted. "Tumor heterogeneity represents a clonal hierarchy in which the different populations compete with each other."

In the center of the hierarchy is the melanoma stem cell. Although melanomas may differ from one patient to the next, they all contain melanoma stem cells. Targeting the stem cell is critical for treatment outcome. "This one cell can give rise to all the others," said Dr. Herlyn. "If we let the cancer stem cell escape, we will always get the cancer back." ■



COURTESY MEENHARD HERLYN, D.SC.

Under suitable conditions, melanoma cells form spheres (shown here at 40X magnification) that are capable of self-renewal and are highly tumorigenic.

Nodular BCC Recurrence High After Photodynamic Therapy

BY TIMOTHY F. KIRN
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LAS VEGAS — Recurrence can be a problem when aminolevulinic acid and light are used to treat patients with nodular basal cell carcinomas, largely because the drug does not penetrate to the deeper nodules, Dr. E. Victor Ross Jr. said at the annual meeting of the American Society of Cosmetic Dermatology and Aesthetic Surgery.

Photodynamic therapy using aminolevulinic acid "is somewhat unpredictable with some of these skin cancers, particularly the nodular ones in the absence of curettage prior to the application," said Dr. Ross, director of the laser and cosmetic dermatology unit at the Scripps Clinic in San Diego.

In a recent study that compared surgical excision to photodynamic therapy at 5 years after treatment in 97 patients who had primary nodular basal cell carcinoma, investigators found a 14% recurrence rate with the light-activated therapy, versus a 4% rate with surgical excision (Arch. Dermatol. 2007;143:1131-6).

'Blue light does not work for those lesions that are further than about a millimeter down.'

DR. ROSS

"We find the relapse rate is reasonably high, so you have to be careful in interpreting the statistics sometimes," he said. Paying attention to certain aspects of treatment, however, can probably improve the results.

In treating skin cancers, the aminolevulinic acid must be applied and left on for at least 4-6 hours before the light application.

For nodular basal cell carcinoma, curettage should be performed on the lesion before applying the aminolevulinic acid, Dr. Ross said.

Removing the stratum corneum, at the very least, is important before applying aminolevulinic acid because it greatly inhibits penetration of the cream, he pointed out.

Use of red light (630 nm) may be better than using blue light (400-450 nm) because it penetrates deeper.

The trade-off, however, is that it does not activate the protoporphyrin-9 created from the aminolevulinic acid as well as blue light, he said at the meeting.

Photodynamic therapy using aminolevulinic acid 'is somewhat unpredictable with some of these skin cancers ... in the absence of curettage.'

From his experience working with a red-light, potassium-titanyl-phosphate (KTP) pump-dye laser, Dr. Ross has found that the red light is preferable.

It is not as much better as it should be, but it is a little better. "Blue light does not work for those lesions that are further than about a millimeter down," he commented.

"Theoretically, red light should work a lot better, despite the fact that [it] does not activate the protoporphyrin-9 as well, simply because it penetrates a lot better," he added.

Dr. Ross said that he uses a cream base for the aminolevulinic acid (specifically Eucerin lotion) instead of the ethanol/water solution that is contained in Levulan Kerastick.

"We get better fluorescence in the basal cells at the treatment time," said Dr. Ross, who reported relevant conflicts of interest involving Palomar Medical Technologies and Alma Laser. ■