

ISET Device

A Useful Tool to Answer Some Questions About the Biologic Behavior of Melanocytic Nevus Cells

IN THIS ISSUE OF THE ARCHIVES, DE GIORGI ET AL¹ report the results of a very original analysis of circulating benign nevus cells in blood samples from a patient with an atypical melanocytic lesion. Their study was based on a new method named *ISET* (isolation by size of epithelial tumor cells) (*ISET Device*; Metagenex, Paris, France). The method was first described by Vona et al² in 2000. Peripheral blood is collected in EDTA, and normal cells are eliminated by filtration through a polycarbonate membrane with calibrated pores of 8 μm .³ Peripheral blood leukocytes are often the smallest cells in the body and can be eliminated by filtration. The retained “large” cells can be counted, stained, and characterized. Further studies, including molecular analysis, can easily be performed. The method is simple, fast, and highly sensitive. It can also detect 1 tumor cell in 1 mL of blood. Pinzani et al⁴ recently demonstrated that circulating melanoma cells can be detected with *ISET*. Tyrosinase messenger RNA (mRNA) levels in blood samples from patients with uveal melanoma were correlated with the number of circulating melanoma cells.⁴ One limitation of the *ISET* technique is that although it can isolate circulating cells by size, morphological features, and immunohistochemical characteristics, it cannot discriminate between malignant and benign cells. However, the presence of genetic mutations associated with malignant potential may also be studied.

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In their study, De Giorgi and coauthors demonstrated the presence of circulating nevus cells in blood samples from a patient with an atypical melanocytic lesion. The identification of these cells was confirmed by morphological analysis and by the detection of *BRAF* (V600E)-mutated DNA and tyrosinase mRNA in plasma. The questions raised by this work are of great interest. The spontaneous circulation of tumor cells is considered the hallmark of their “invasive behavior.” Detection and quantification of circulating tumor cells may provide a prognostic factor in patients with cancer and could help to define a subgroup of patients who may benefit from additional treatment. However, the mechanisms leading to angiotropism, intravasation, and circulation in the bloodstream are still poorly understood. In epithelial tumors, an “epithelial to mesenchymal transition” seems to be a critical step in the development of metastasis.³ Angiotropism is well known

in metastatic melanoma and reflects tumoral cell behavior. Angiotropism was shown to be an independent predictor of local recurrence and in-transit metastasis in primary cutaneous melanoma⁵; however, in cutaneous melanocytic nevi, angiotropism is merely considered an anecdotal finding. Its frequency varies from 30% to 100% of cases, depending on the size of the melanocytic nevi and the age of the patients.⁶ Hematogenous circulation of benign nevus cells may explain the presence of nevus cells in the placenta and the “benign metastases” associated with melanocytic nevi.

De Giorgi and colleagues’ report may raise the question of the validity of demonstrating circulating melanocytes, especially in patients with both melanoma and melanocytic nevi. It would be of interest to compare the value of circulating melanocytes in patients with melanoma with or without an atypical mole syndrome. Furthermore, the biomarkers used in their study (*BRAF* mutation and tyrosinase mRNA) are not specific for malignant melanoma cells. More specific melanoma markers, either genomic (eg, methylation of *PTEN* or *NRAS* mutation) or the presence of specific melanoma transcripts such as osteopontin or *RGSI*, could be assessed in circulating cells from patients with metastatic melanoma.^{7,8}

Is a hematogenous migration of benign nevus cells anecdotal or a characteristic of congenital or embryogenic melanocytic nevus cells? We may postulate that neural crest cells could use blood circulation during embryogenesis. Barnhill et al⁶ recently suggested that extravascular migration of melanocytes could explain the development of congenital nevi. Metastasis and hematogenous dissemination of tumoral melanocytes (as compared with the epidermal to mesenchymal transition) could illustrate a reversion to embryogenic melanocytes or the presence of melanocytic stem cells.

Some results are also disappointing. De Giorgi and coauthors analyzed 3 blood samples, and nevus cells were found only after removal of the nevus. The possibility of hematogenous tumor cell dissemination during intraoperative manipulation gives cause for concern. The intraoperative risk of hematogenous dissemination of melanoma is being evaluated for the surgical treatment of liver metastases. Schmidt et al⁹ reported on the protocol of a multicenter, prospective, randomized, controlled study to evaluate whether surgical resection techniques of liver metastases influence hematogenous tumor cell dissemination. At this time, we are not aware of similar research regarding surgical resection of the cutaneous site of the melanoma.

The ISET technique is simple and powerful. These very interesting new results (based on only 3 blood samples¹) need to be confirmed in other patients and notably in cases involving other noncongenital benign melanocytic lesions. Also, the future development of specific genetic melanoma biomarkers will probably help to differentiate melanoma and nonmalignant pigmented circulating cells. We are certain that in the future ISET will provide further information about the significance of circulating melanocyte cells in the bloodstream and will add to our knowledge regarding the biologic behavior of melanocytic cells.

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REFERENCES

1. De Giorgi V, Pinzani P, Salvianti F, et al. Circulating benign nevus cells detected by ISET technique: warning for melanoma molecular diagnosis. *Arch Dermatol.* 2010;146(10):1120-1124.
2. Vona G, Sabile A, Louha M, et al. Isolation by size of epithelial tumor cells: a new method for the immunomorphological and molecular characterization of circulating tumor cells. *Am J Pathol.* 2000;156(1):57-63.
3. Paterlini-Brechot P, Benali NL. Circulating tumor cells (CTC) detection: clinical impact and future directions. *Cancer Lett.* 2007;253(2):180-204.
4. Pinzani P, Mazzini C, Salvianti F, et al. Tyrosinase mRNA levels in the blood of uveal melanoma patients: correlation with the number of circulating tumor cells and tumor progression. *Melanoma Res.* 2010;20(4):303-310.
5. Van Es SL, Colman M, Thompson JF, McCarthy SW, Scolyer RA. Angiotropism is an independent predictor of local recurrence and in-transit metastasis in primary cutaneous melanoma. *Am J Surg Pathol.* 2008;32(9):1396-1403.
6. Barnhill RL, Chastain MA, Jerdan MS, Lebbé C, Janin A, Lugassy C. Angiotropic neonatal congenital melanocytic nevus: how extravascular migration of melanocytes may explain the development of congenital nevi. *Am J Dermatopathol.* 2010;32(5):495-499.
7. Mirmohammadsadegh A, Marini A, Nambiar S, et al. Epigenetic silencing of the PTEN gene in melanoma. *Cancer Res.* 2006;66(13):6546-6552.
8. Gogas H, Eggermont AM, Hauschild A, et al. Biomarkers in melanoma. *Ann Oncol.* 2009;20(suppl 6):vi8-vi13.
9. Schmidt T, Koch M, Antolovic D, et al. Influence of two different resection techniques (conventional liver resection versus anterior approach) of liver metastases from colorectal cancer on hematogenous tumor cell dissemination—prospective randomized multicenter trial. *BMC Surg.* 2008;8:6.

Gap-Based Education, Changing Competence, and Dermatology Simulation

A Glimpse at the Future of CME

IN THIS ISSUE OF THE ARCHIVES, ROBINSON ET AL¹ describe a simulation module using artificial skin lesion moulages that compare student diagnoses of suspect acral lesions in non-Hispanic white and black patients. In doing so, the authors provide readers with a glimpse of continuing medical education (CME) of the future.

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In 2006, the Accreditation Council for Continuing Medical Education (ACCME),² the credentialing body for CME in the United States, published new criteria for CME providers. The new requirements were instituted, in part, to address the ineffectiveness of most of the current CME programming at measurably changing physician behavior. Traditional lecture-based CME, while reportedly sat-

isfying most physicians, has very little effect on physician performance or patient health outcomes³ despite its high costs—in 2008, the ACCME^{4,5} estimates that \$2.37 billion was spent on CME in the United States, or approximately \$3600 per US physician!

Many hospitals, institutions, and professional societies of practicing dermatologists in the United States are CME providers, and they must design CME activities to fulfill the new 2006 requirements.² Dermatologists seeking CME will soon find a different, and presumably more effective, approach. Whereas most current CME provides little more than documentation of attendance, future CME will require a greater accountability to show changes in competence, performance, and ultimately, changes in patient outcomes.⁶ There will necessarily be a shift toward the “backward planning” of CME activities based on practice gaps. The education project de-