Slowly proliferating melanoma cells with high metastatic properties

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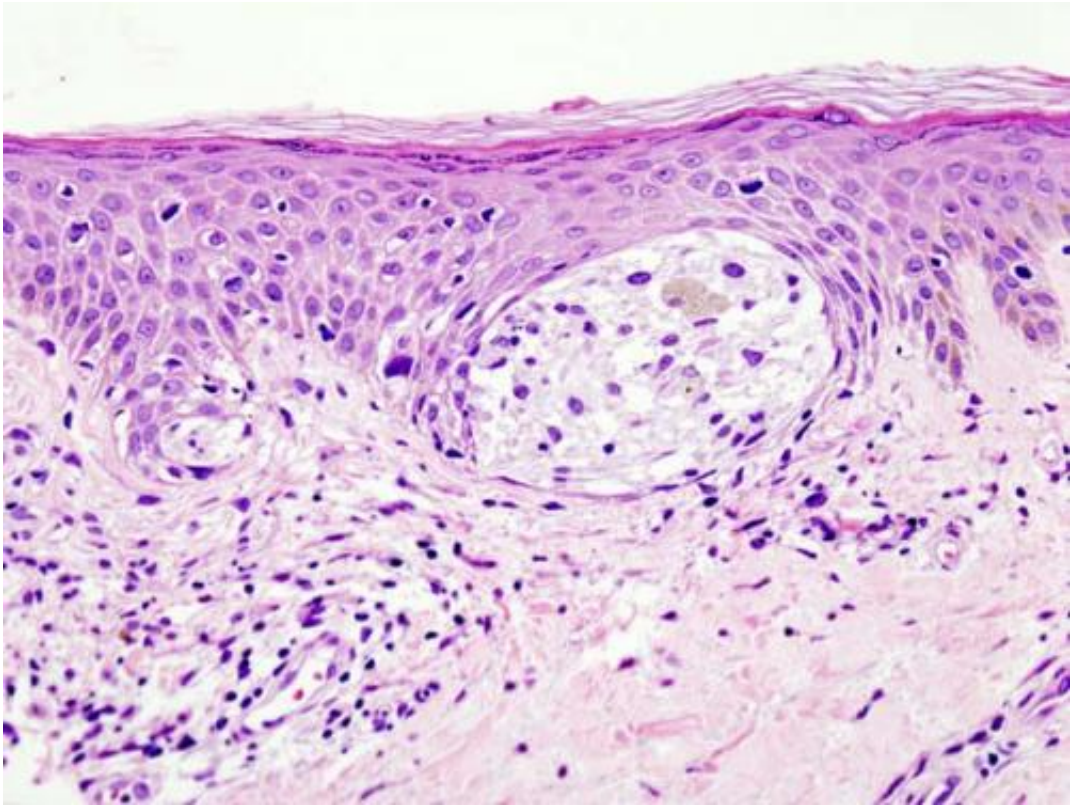

Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

A study conducted at The Wistar Institute has led to the identification of a slowly proliferating and highly invasive melanoma cell subpopulation, characterized by production of a protein associated with invasive behavior. The research was published in the journal *Oncogene*.

The pattern of metastatic dissemination in advanced melanoma is unpredictable because of the biological and genetic heterogeneity that characterizes melanoma cells. Specifically, they differ in their proliferation rates, ability to invade other tissues and interaction with the surrounding microenvironment.

"Understanding the biological events that take place at distant sites from the primary tumor is crucial for preventing or slowing metastasis," said lead researcher Meenhard Herlyn, D.V.M., D.Sc., Caspar Wistar Professor in Melanoma Research and director of The Wistar Institute Melanoma Research Center. "Our new findings suggest that we need to adjust our treatment strategies for early disease and target individual, disseminating tumor cells that we are likely missing with the current diagnostic techniques."

Previous research in the Herlyn lab has shown the existence of a slowly proliferating population of melanoma cells that is required for tumor maintenance. In the new study, Herlyn and colleagues characterized the invasive properties of this slowly proliferating population, demonstrating its ability to leave the primary tumor and disseminate rapidly to distant sites.

The cells were tracked based on their ability to retain a fluorescent dye. Following fluorescence labeling of the whole cell population, the fluorescence intensity decreases by half at each cell division and gets diluted out and disappears in fast-dividing cells, whereas the signal is retained longer in dormant or slowly dividing cells. By utilizing this technique, the researchers were able to determine that the slowly proliferating melanoma cells have a highly invasive behavior in vivo. After injection in immunocompromised mice, the fluorescence disappears rapidly from the primary tumor and emerges at distant sites. Importantly, some of the slowly proliferating cells retain the fluorescent label long after colonizing other tissues, indicating that they can remain

dormant for long periods of time and regain proliferative capacity at a later stage, eventually leading to metastasis.

No correlation was found between the low proliferative, highly invasive state and the most common genetic alterations that cause melanoma, indicating that the slowly proliferating population is genetically heterogeneous. However, through proteomic analysis, Herlyn and colleagues found that the slowly proliferating cells express higher levels of the protein SerpinE2, which has a pro-invasive role in other types of cancer. They also demonstrated that SerpinE2 is critical for melanoma invasion and its expression levels in melanoma patients correlate with tumor progression.

"SerpinE2 is expressed by melanoma cells and not by normal skin cells," said Michela Perego, Ph.D., an associates staff scientist at Wistar and first author of the study. "Therefore, it may be a potential useful tool for early detection of isolated malignant cells that have left the primary tumor and colonized distant organs and possibly a novel target to prevent or limit melanoma dissemination."

"This concept may sound counterintuitive because we are used to the idea that cancer cells are highly proliferative," added Herlyn, also professor in Wistar's Molecular and Cellular Oncogenesis Program. "However, slowly proliferating melanoma cells are more aggressive and therefore the most dangerous ones."

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