Researchers develop more efficient approach to create mouse models

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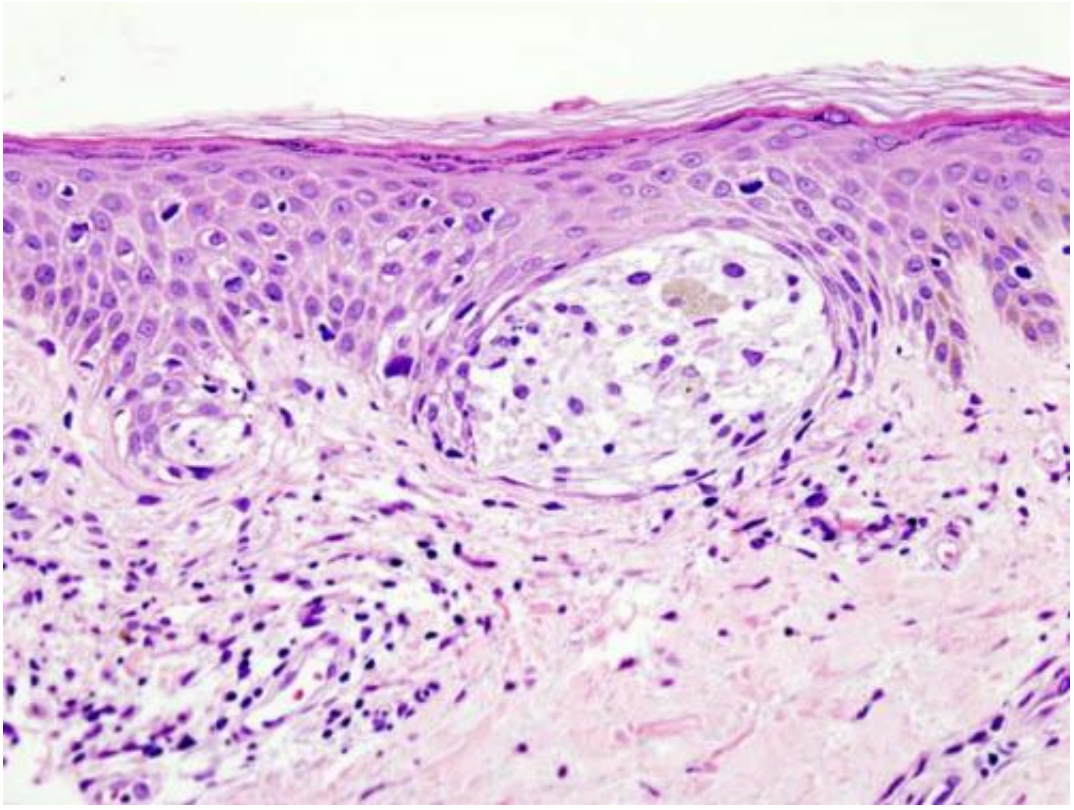

Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

Genetically engineered mouse models are often used by scientists to study how the addition, deletion or mutation of genes affects the development of disease and effects of drugs. The process of creating these genetically modified mice is extremely time consuming and

expensive, which limits the ability of scientists to use their models to perform important research. Moffitt Cancer Center researchers have developed a new platform for creating genetically engineered mice to study melanoma that is significantly faster than a normal mouse model approach. Their work was published in *Cancer Research*.

Mouse models have enabled numerous advances in our understanding of cancer and potential treatment approaches. Scientists can add or delete genes (alleles) from particular types of cells in mice, such as melanocytes in the skin, with tissue-specific DNA-targeting approaches. Additionally, scientists often make multiple changes in different genes at the same time to determine how multiple genetic alterations affect outcomes, or they may turn genes on or off during predetermined periods of time during the mouse's life to assess how time-dependent alterations impact disease and drug treatments.

Despite the knowledge gained from mouse models, "creating mouse alleles and breeding multi-allelic melanoma-prone experimental mice is expensive, slow, and cumbersome, rendering conventional mouse modeling an inefficient method to study gene functions in vivo," explained Florian Karreth, Ph.D., assistant member of the Department of Molecular Oncology at Moffitt.

Karreth and his team wanted to develop a more efficient method of creating mice with multiple genetic modifications in melanocytes. They began by isolating embryonic stem cells from previously created genetically modified mice that had alterations in genes known to contribute to melanoma (BRAF, NRAS, PTEN and CDKN2A). Next, the researchers modified genes of these embryonic stem cells even further in laboratory cultures and injected them into embryos from the original mouse strain. These embryos were then implanted into female mice and eventually were born as chimeric mice with multiple genetic alterations.

The researchers determined that the chimeric mice were able to develop melanomas to a similar extent as mice created through the normal approach. They used their new platform to show how modulation of PTEN gene expression could affect the development and progression of melanoma, and also created melanoma cell lines from the chimera mice that could be used in laboratory experiments.

Karreth hopes that the new platform will benefit the scientific community as a whole and have allowed both the embryonic stem cells lines and the melanoma cell lines to be available to the entire melanoma research community. "Given that it takes less than 2.5 months from embryonic stem cell targeting to inducing melanomagenesis in experimental chimeras, we anticipate that our platform has the potential to dramatically accelerate melanoma studies in mice," he said.

More information: Ilah Bok et al, A versatile ES cell-based melanoma mouse modeling platform, *Cancer Research* (2019). DOI: 10.1158/0008-5472.CAN-19-2924

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