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Targeting telomeres to overcome therapy resistance in advanced melanoma

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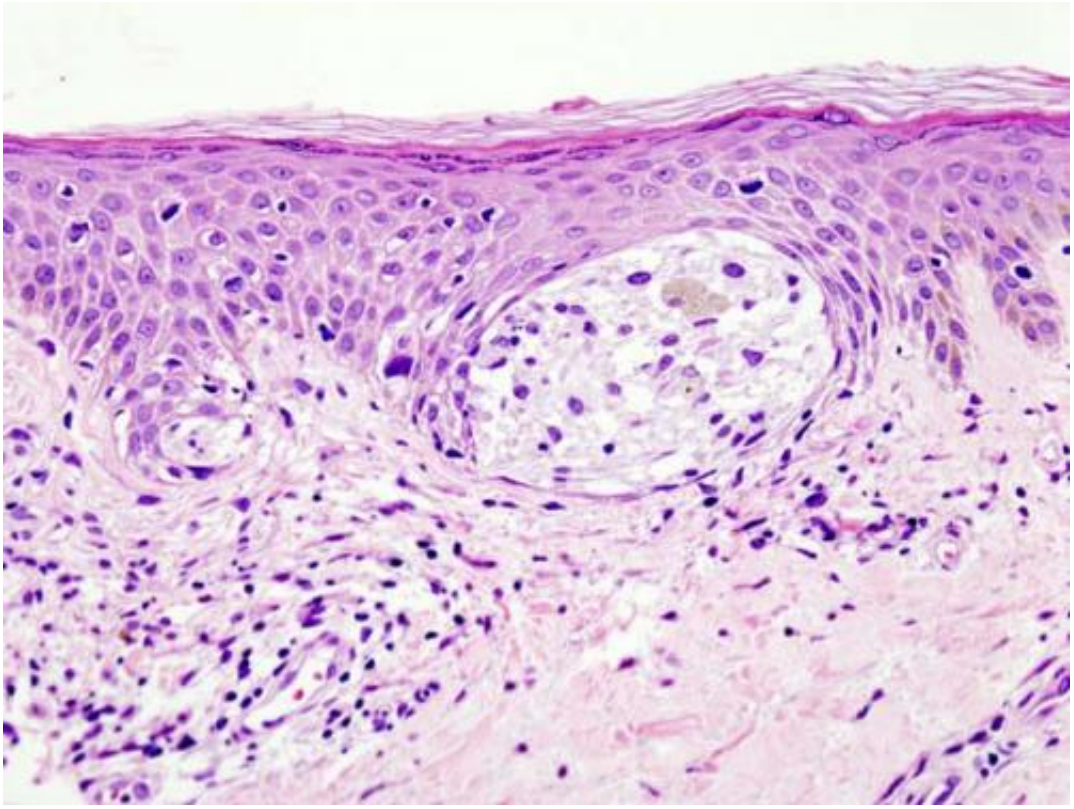

Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

A study conducted at The Wistar Institute in collaboration with The University of Texas Southwestern Medical Center has demonstrated the efficacy of targeting aberrantly active telomerase to treat therapy-resistant melanoma. The research was published in the journal *Clinical*

Cancer Research.

The introduction of targeted therapies and immune checkpoint blockade therapies has revolutionized the therapeutic options for patients with advanced melanoma. However, the long-term therapeutic benefit of these new approaches is still hindered by the onset of therapy resistance, which can develop through different mechanisms.

A hallmark of several cancer types, including melanoma, is the aberrant regulation of telomerase activity due to mutations in the regulatory element of the telomerase gene, which results in increased production of the protein. Telomerase is an enzyme responsible for protecting the integrity of chromosome ends during replication. While it is absent in most normal adult cells that don't actively proliferate, telomerase is reactivated in cancer cells, allowing continuous cell divisions and making them immortal.

"Our work presents pre-clinical evidence that targeting the aberrant telomerase activity may provide a universal strategy to overcome therapy resistance and achieve long-term melanoma control," 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.

Herlyn and his collaborators used a modified telomerase substrate they had previously described, called 6-thio-dG, to impair telomerase activity by inducing telomere dysfunction. They showed that 6-thio-dG induced cell death in melanoma cells carrying mutations in the BRAF gene without affecting the viability of normal skin cells, and it impaired the growth of several BRAF-mutant melanoma cell lines transplanted in mice. The BRAF gene is mutated in approximately half of all cases of melanoma.

The team also studied the ability of 6-thio-dG treatment to stop proliferation and tumor growth of therapy-resistant melanoma cells. They created a large panel of human melanoma cell lines with acquired resistance to targeted therapy and immunotherapy and showed a general sensitivity of these cells to 6-thio-dG both in vitro and in vivo in mouse models.

"Our results add to the mounting evidence supporting the existence of an important relationship between telomeres and telomerase and cancer," said Gao Zhang, Ph.D., a staff scientist in the Herlyn Lab and first author of the study. "Our data suggest that 6-thio-dG may be used either as monotherapy following first- and second-line therapies to prolong disease control after onset of resistance, or in combination with first-line therapies to overcome intrinsic resistance."

Provided by The Wistar Institute

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