Discovery of four subtypes of melanoma points to new treatment approaches

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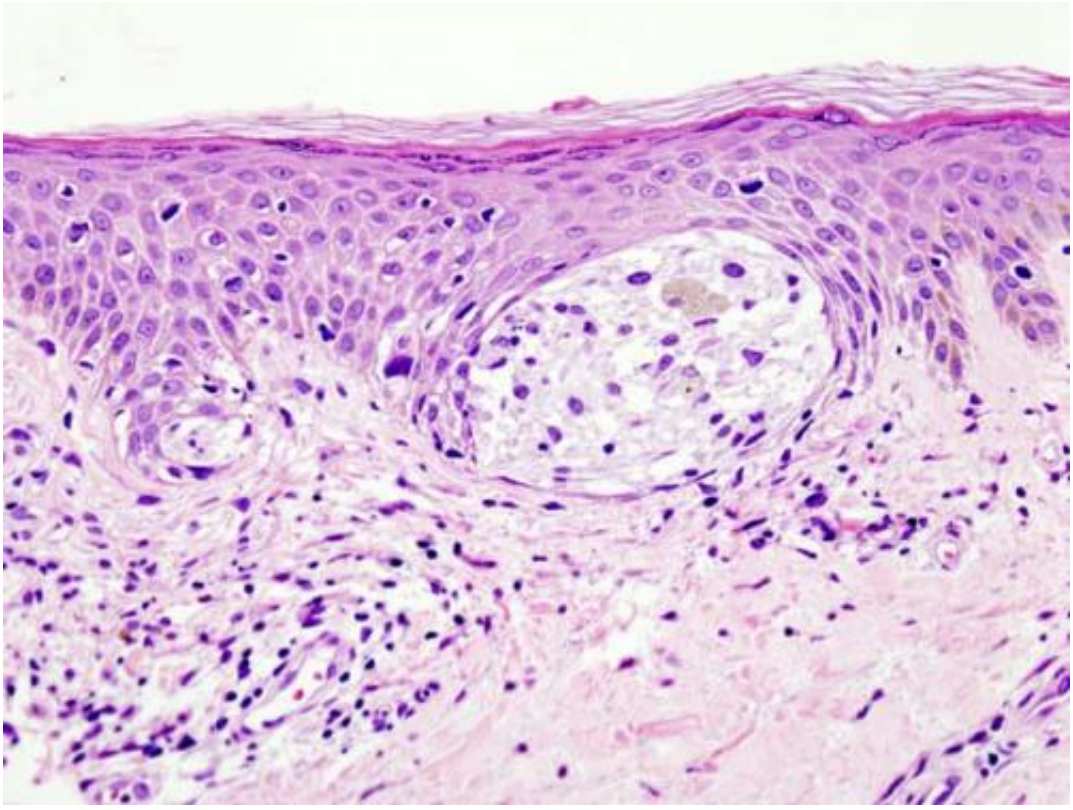

Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

Melanoma, a relatively rare but deadly skin cancer, has been shown to switch differentiation states—that is, to regress to an earlier stage of development—which can lead it to become resistant to treatment. Now, UCLA researchers have found that melanomas can be divided into four

distinct subtypes according to their stages of differentiation. Cell subtypes that de-differentiated—meaning that they reverted back to a less-mature cell—showed sensitivity to a type of self-inflicted cell death called ferroptosis.

The research also showed that certain subtypes of melanoma cells could be successfully treated using multiple cancer therapies in combination with ferroptosis-inducing drugs.

Melanoma arises from melanocytes, cells that produce pigments. Although targeted therapies and a greater understanding of cancer immunology have significantly improved survival, many patients either relapse or do not respond to treatment.

The UCLA team, led by Dr. Thomas Graeber, analyzed the gene expression of melanoma cells and compared them to information in public genetic databases to identify the four different subtypes of melanoma with different drug sensitivities. The team organized the melanoma cells according to characteristic patterns of genes turned on by the cells. Comparing the gene expression patterns to data from stem cells induced to differentiate into melanocytes, they found that melanomas can be categorized into four distinct differentiation states.

"This refined characterization improves our understanding of the progressive changes that occur in melanoma cells during dedifferentiation, which can help develop better strategies to target this form of therapy resistance," said Jennifer Tsoi, who was a member of the research team as a UCLA graduate student and now is a postdoctoral fellow at UCLA.

The investigators then searched pharmacogenomics databases for compounds that could best be used to treat melanomas characterized by the dedifferentiation expression pattern, either individually or in

combination with other drugs.

The study introduces a new area of therapeutic possibilities for melanoma, because it is the first to link ferroptosis to melanoma differentiation states. It also more precisely defines different subtypes of melanoma, based on specific gene expression and metabolic profiles. Those subtypes characterize four steps along a trajectory taken by melanoma cells as they respond to exogenous stresses, such as drug treatments.

The approach for targeting dedifferentiated melanomas could complement existing standard-of-care therapies, since kinase inhibitors and immunotherapies are much more effective against differentiated cells than de-differentiated cells.

"Furthermore, these standard-of-care therapies can induce dedifferentiation, and thus in a co-treatment setting, ferroptosis induction can potentially block melanoma cells attempting to take this escape route," Graeber said.

The research is published online in *Cancer Cell*.

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