Aggressive melanoma cells at edge of tumours are key to cancer spread

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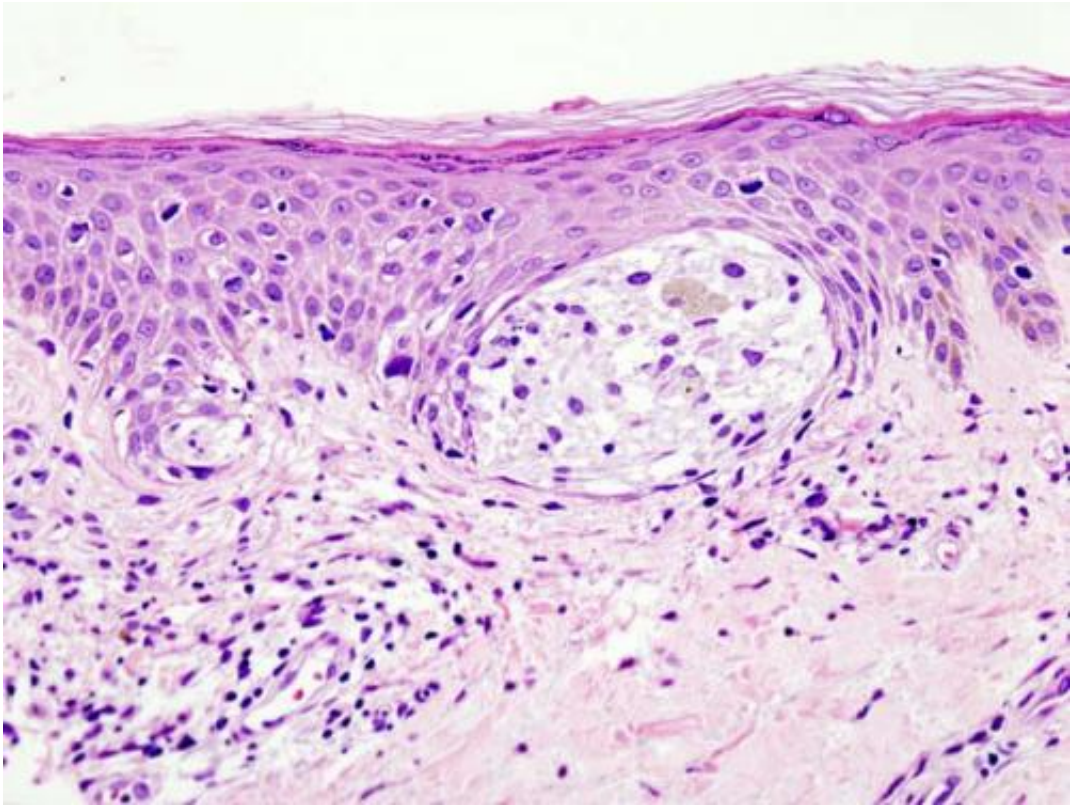

Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

Research led by Queen Mary University of London has revealed novel insights into the mechanisms employed by melanoma cells to form tumors at secondary sites around the body. The findings from the study may help to identify new targets to inhibit melanoma spread and guide

treatment decisions in the clinic.

Melanoma is an aggressive type of skin cancer, and melanoma cells disseminate easily through the body even at early stages of the disease. The spread of cancer from one site in the body to another in a process called metastasis is the leading cause of cancer mortality. In order for cancer to metastasise, cancer cells must break off from the primary tumor, travel through the bloodstream or lymph system, settle in a new site within the body and grow into a new tumor.

The findings of this study, published today in *Nature Communications*, revealed that there is a highly invasive subset of melanoma cells located around the edge of the tumor, called 'rounded-amoeboid' cells, that not only disseminate through the body very efficiently, but are also very successful at forming new tumors.

Dr. Irene Rodriguez Hernandez from Queen Mary University of London, first author of the study said: "An important observation of our study was that aggressive melanoma cells were not only very invasive but were good at dividing. Therefore, such melanoma cells were capable of growing new tumors both in the skin and at a distant site such as the lung. Our work sheds some light on the ability of melanomas to form metastases very early in the progression of the disease."

New tumor formation initiated by a powerful set of signals

By using melanoma cell lines and preclinical models, the team found that melanoma cells can initiate tumors at new sites via a powerful signaling cascade. Melanoma cells produce a molecule called Wnt11, which binds to a second molecule on the surface of the cancer cells called FZD7. Once bound, these molecules activate a protein called DAAM1, which in

turn controls a protein called Rho A—a master regulator of cancer invasion. This set of events allows melanoma cells to invade surrounding tissue and makes them more capable of growing new tumors when they reach new sites within the body.

Interestingly, these signaling molecules are also important during human development from the embryo. Melanoma originates from the pigment-producing cells within the skin called melanocytes, which are formed from a set of cells called neural crest cells. Neural crest cells are highly migratory; they move around to different regions of the body to give rise to many different cell types during human development.

Professor Victoria Sanz-Moreno from Queen Mary University of London who led the study, said: "The molecules that melanoma cells use to become invasive and to grow are important for neural crest functions during human development. We have uncovered a mechanism by which cancer cells hijack this developmental program to become aggressive. It is a bit like melanoma has a 'cellular memory' to revert to that neural crest state."

To determine if their laboratory findings were representative of melanoma in the clinic, the team analyzed samples from primary tumors in melanoma patients. Their analyses revealed that the edges of melanoma tumors were enriched with rounded-amoeboid cells that expressed the signaling molecules that promote both growth and invasion.

More information: "WNT11-FZD7-DAAM1 signalling supports tumour initiating abilities and melanoma amoeboid invasion" by Dr. Sanz Moreno. *Nature Communications*. DOI: 10.1038/s41467-020-18951-2

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