Study links genetic mutation and melanoma progression

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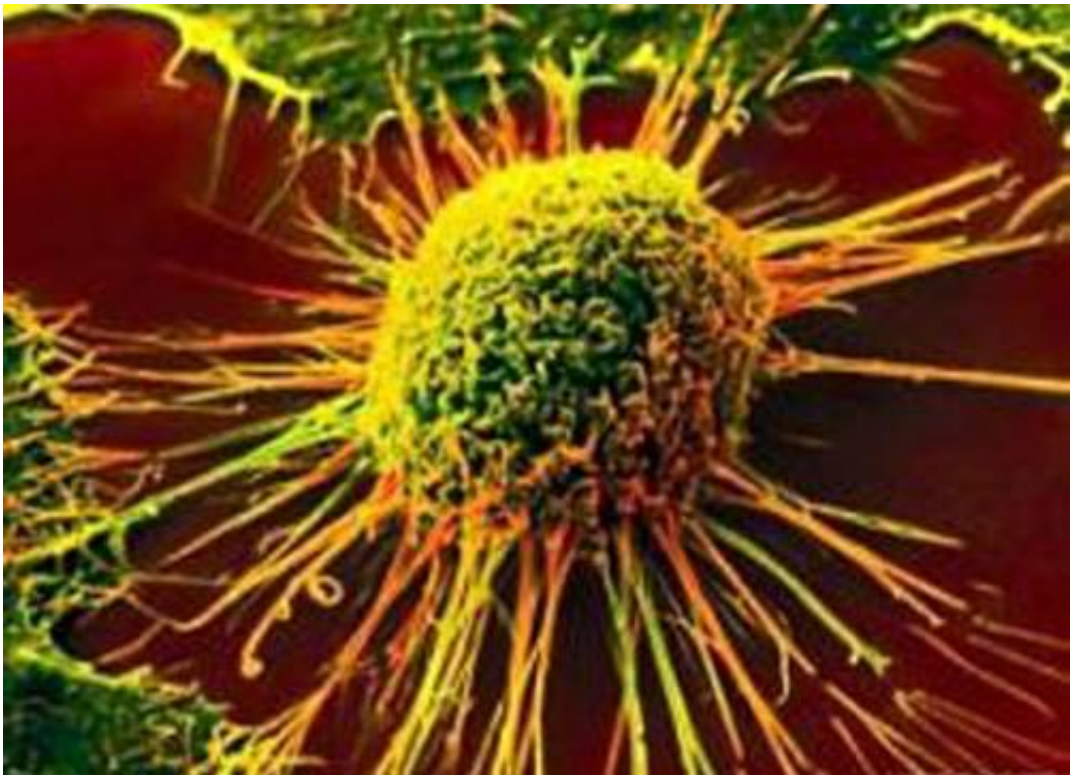

Dartmouth researchers have found that the genetic mutation BRAFV600E, frequently found in metastatic melanoma, not only secretes a protein that promotes the growth of melanoma tumor cells, but can also modify the network of normal cells around the tumor to support the disease's progression. Targeting this mutation with Vemurafenib

reduces this interaction, and suggests possible new treatment options for melanoma therapy. They report on their findings in "BRAFV600E melanoma cells secrete factors that activate stromal fibroblasts and enhance tumourigenicity," which was recently published in *British Journal of Cancer*.

Authors of the study are Dr. Chery A. Whipple, research associate at the Geisel School of Medicine at Dartmouth, and Dr. Constance Brinckerhoff, professor of Medicine and of Biochemistry at Geisel and member of Dartmouth-Hitchcock Norris Cotton Cancer Center.

"This work supports the importance of the tumor cells "talking" with the normal cells present in the tumor microenvironment," said Whipple, first author on the study. "Targeting the tumor cells with specific therapy to reduce the secreted proteins can reduce the aggressive behavior of the tumor and inhibit disease progression."

Melanoma, the most lethal form of skin cancer, is responsible for more than 80 percent of all skin cancer deaths and spreads readily to the lymph nodes and other organs. While early stage melanoma is curable, the later vertical growth phase (VGP) is frequently metastatic, with median survival times of less than nine months. Melanoma that progresses to this stage is often associated with the gene mutation BRAFV600E, which is found in about 50 percent of melanomas. This BRAF mutation activates certain enzyme pathways that are involved in many cell processes.

Using genetically engineered melanoma cell lines and xenograft mouse models, the Dartmouth researchers found that BRAFV600E melanoma cells expressed higher levels of several cytokines (proteins that act on the immune system and can be used to help the body fight cancer) and Matrix Metalloproteinase-1 (MMP-1; MMPs are associated with various processes including tissue repair and metastasis). Their study also

suggests a mechanistic link between BRAFV600E and MMP-1 that modifies the network of normal cells surrounding melanoma tumors, making these "normal cells" more supportive of tumor growth and development. Vemurafenib, a therapeutic drug that specifically targets the BRAFV600E mutation, is able to reduce the expression of several proteins essential for activating this interaction.

"Given that our data show that Vemurafenib is able to reduce the expression of several proteins that are essential for activating the tumor microenvironment (TME), a next step would be to ask whether Vemurafenib normalizes the TME, or keeps it from becoming activated," said Whipple. "If so, does it create a window of time where we could target the TME, normalize it, and enhance the patient's therapeutic response?"

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