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Molecular differences between early and advanced melanomas could provide new drug targets

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The cell-signaling molecule Akt is a primary trigger that leads malignant melanomas on the skin's surface to begin growing vertically beneath the skin and turn into deadly invasive cancers, scientists have found. Understanding this key molecular difference between radial melanomas that spread on the surface of the skin and melanomas that grow vertically and invasively could provide new targets for the development of drugs to treat individuals with advanced stage melanomas.

Radial melanomas that have not spread below the skin can be treated surgically and have a survival rate of 98 percent beyond five years, according to the American Cancer Society. But when melanomas grow downward, the tumors become highly resistant to chemotherapy and radiation and the five-year survival rate falls rapidly, to 64 percent if the disease has reached the lymph nodes and 16 percent if it has spread to other organs.

The discovery of Akt's significant role in the progression of melanomas was made by scientists in the Department of Dermatology at Emory University School of Medicine and published in the March issue of the *Journal of Clinical Investigation*. Senior author is Jack L. Arbiser, MD, PhD, and lead author is Baskaran Govindarajan, PhD.

When the scientists introduced the gene for Akt into radial growth melanoma cells, the cells expressed nearly eight times as much of the

growth factor protein VEGF. VEGF is known to be a powerful stimulator of angiogenesis Ð the growth of microscopic blood vessels that nourish cancerous tumors and lead to unregulated cell growth. When melanoma cells overexpressing Akt were introduced into immunocompromised (nude) mice, the mice developed aggressive tumors that expressed high levels of VEGF, whereas a control group of mice developed no tumors.

Another result of Akt overexpression was the increased production of reactive oxygen (ROS). Reactive oxygen is created during cellular metabolism and has long been associated with triggering angiogenesis and the resulting growth of tumors. The scientists also found that the Akt-induced melanoma cells produced more of the enzyme NOX4, one of the NOX family of genes known to increase generation of ROS and to trigger angiogenesis.

The scientists also found that in cells with greater Akt expression, there was an increase in impaired mitochondria-- the energy factories of cells. Their research showed, however, that these mutations in mitochondria were likely the result of the prolonged exposure to increased oxidative stress caused by Akt overexpression, but that the mitochondrial mutations were not essential for the aggressive growth of melanomas induced by Akt.

"Our research shows that Akt overexpression on its own is sufficient to transform radial growth melanoma cells into highly invasive tumors via reactive oxygen pathways," says Dr. Arbiser. "This could provide us with promising targets for anti-cancer drug therapy. We will continue to work on refining the exact mechanisms of how Akt influences the aggressive growth of melanomas."

Source: Emory University