

# Tumor target suggests personalized treatment for melanoma

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Identification of a key player in a signaling pathway involved in the development of melanoma - the deadliest form of skin cancer - may offer hope for new targeted melanoma therapies.

Ann Richmond, Ph.D., and colleagues at Vanderbilt-Ingram Cancer Center report that a signaling molecule, known as IKK $\beta$ , is essential for melanoma tumor development in a mouse model of the disease. The results, published June 7 in the *Journal of Clinical Investigation*, also point to ways of targeting therapies that inhibit IKK $\beta$  toward the patients most likely to benefit from them based on their genetic profile.

Melanoma is the deadliest form of [skin cancer](#) and incredibly difficult to treat successfully once the tumor has spread beyond the skin.

Prior studies have shown that the NF- $\kappa$ B signaling pathway - centered on the protein NF- $\kappa$ B, which regulates gene expression - is abnormally activated in tumor cells; the pathway is turned "on" constantly, even at times it should be turned "off." This activation often results from abnormal activation of another enzyme in the pathway, IKK $\beta$ .

Just how NF- $\kappa$ B contributes to tumor progression has been unclear. And with drugs that inhibit this pathway entering clinical trials, a clearer picture of its function in tumor progression is needed.

To better understand the role of this pathway - in particular, of IKK $\beta$ 's role - Richmond's lab developed a mouse model that mimics the genetic

alterations involved in melanoma development in humans.

Jinming Yang, Ph.D., a staff scientist in Richmond's lab, led the effort to generate these mice, which lack the tumor suppressor INK4a/ARF (commonly lost in melanomas) and have the Ras/Raf pathway activated (which is activated in about 70 percent of melanoma lesions).

The researchers then added the ability to "turn off" IKK $\beta$  only in melanocytes, the pigment-producing skin cells in which melanomas initiate, simply by treating the mice with an antibiotic.

Mice with normal IKK $\beta$  activity developed "loads and loads of melanoma tumors all over their bodies...on the tail, the ear, and anywhere melanocytes are," said Richmond, an Ingram Professor of Cancer Biology at Vanderbilt University Medical Center and a senior career research scientist with the Department of Veterans Affairs.

But mice in which IKK $\beta$  was "turned off" developed no melanoma tumors.

They also found that treating mice with normal IKK $\beta$  activity with small molecule inhibitors of the enzyme could inhibit the growth of melanoma lesions.

"This shows for the first time that you have to have IKK $\beta$  for Ras-induced melanoma, suggesting that there's a way to specifically target melanoma lesions," she said.

However, the experiments identified an important caveat: blocking IKK $\beta$  only seemed to protect against melanoma formation when another tumor suppressor, p53, is expressed.

Since mutations that disrupt p53 are sometimes found in melanomas,

this suggests that therapies targeting IKK $\beta$  or the NF- $\kappa$ B pathway in general would need to be limited to tumors with normal p53.

Richmond cautions, "With NF- $\kappa$ B inhibitors entering clinical trials at this time, it is imperative that these data be taken into consideration for patient selection or evaluation of response in these trials."

Richmond is collaborating with Vanderbilt-Ingram Cancer Center investigators Mark Kelley, M.D., and Jeffrey Sosman, M.D., to identify, in human tumor samples, which tumors would respond to targeted inhibitors of the Ras/Raf and NF- $\kappa$ B pathways.

Such information could aid in diagnosis and "be used to deliver personalized medicine" to [melanoma](#) patients in the future, she said.

"We're passionate about (IKK $\beta$  inhibitors) possibly going forward, maybe not as a single agent, but in combination (treatments). As we are able to better predict which patients will respond to which drugs, there's real hope there."

Provided by Vanderbilt University Medical Center

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