

# Researchers identify super-oncogenic protein that promotes development of melanoma

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Ze'ev Ronai, Ph.D., chief scientific advisor of SBP and lead author of the study.  
Credit: Sanford Burnham Prebys Medical Discovery Institute

An international collaborative study led by scientists at the Sanford Burnham Prebys Medical Discovery Institute (SBP) has identified a malicious form of a protein that drives the formation of melanoma. The findings, published today in *Cell Reports*, reveal unexpected insight into how this lethal skin cancer develops and progresses, and may help

understand and develop novel therapies against these aggressive tumors.

"We found that an inactive version of a protein called activating transcription factor 2 (ATF2) elicits a tumor-promoting effect in a way not seen before," said Ze'ev Ronai, Ph.D., chief scientific advisor of SBP and professor of its NCI-designated Cancer Center. "We have known for years that the active version of ATF2 promotes [melanoma](#), but this result was a surprise because we thought ATF2 transcriptional activity was essential to activate [cancer](#)-related genes."

Ronai's team has been studying ATF2's role in melanoma for two decades. Their past work led to the view that it's dangerous when it's in the nucleus because it controls cancer-enabling genes, but benign when it's not.

In the current study, researchers looked at the oncogenic potential of a 'dead' form of ATF2 in mice with mutations in BRAF, a kinase that transmits signals promoting cell division and is often mutated in pigmented skin cells. The same mutation is found in about half of all human melanomas.

"Inactive ATF2, in mice with mutant BRAF, resulted in the formation of pigmented lesions and later, melanoma tumors," said Ronai, senior author of the study.

"What makes this discovery relevant to human melanoma is that we identified a structurally similar form of inactive ATF2 in human melanoma samples that has the same effects on cancer cells," added Ronai. "Inactive ATF2 could be an indicator of tumor aggressiveness in patients with BRAF mutations, and maybe other types of cancer as well."

"Unlike models with more complex genetic changes, like the inactivation of PTEN and p16 combined with BRAF mutations that result in rapid

tumorigenesis (within a few weeks), the inactive ATF2 caused BRAF mutant mice to develop melanoma much slower, more similar to the timescale seen in patients," commented Ronai. "This improves our ability to monitor the development of melanoma and efficacy of possible interventions."

"We're now investigating why inactive ATF2 so potently promotes BRAF-mutant melanoma, and looking for other types of cancer where it acts the same way," Ronai said. "Our findings may guide precision therapies for tumors with mutant ATF2."

Provided by Sanford-Burnham Prebys Medical Discovery Institute

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