Team finds mechanism linking key inflammatory marker to cancer

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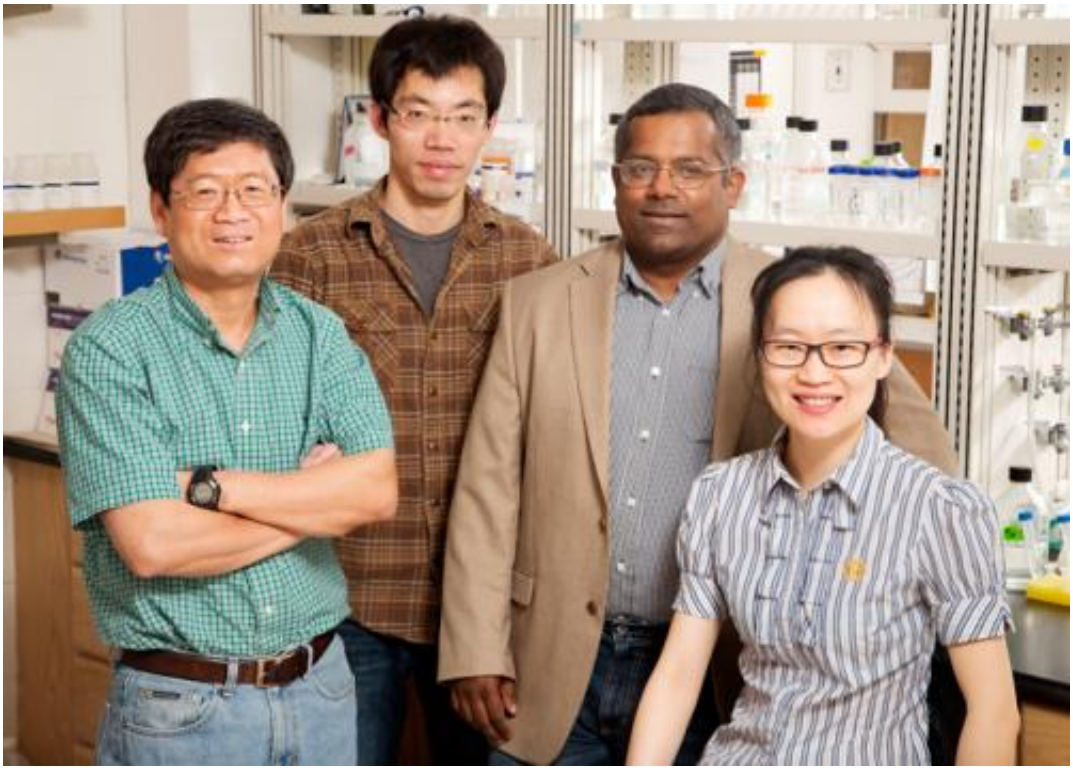

University of Illinois medical biochemistry professor Lin-Feng Chen (left), postdoctoral researcher Xuewei Wu, biochemistry professor Satish Nair, postdoctoral researcher Zhenhua Zou and their colleagues discovered a mechanism by which the inflammatory protein NF-kappa B is activated and contributes to some cancers. Credit: L. Brian Stauffer

In a new study described in the journal *Oncogene*, researchers reveal how a key player in cell growth, immunity and the inflammatory response can

be transformed into a primary contributor to tumor growth.

Scientists call this Jekyll-and-Hyde molecule NF-kappa B. In healthy cells, it is a powerful "first responder," a vital part of the body's immune and inflammatory responses. It spends most of its life in the cell's cytoplasm, quietly awaiting orders. But when extracellular signals – of a viral or bacterial invasion, for example – set off chemical alarms, the cell unchains this warhorse, allowing it to go into the nucleus where it spurs a flurry of defensive activity, including the transcription of genes that trigger inflammation, promote cell proliferation and undermine cell death.

Researchers have known for years that a hyperactive form of NF-kappa B that gets into the nucleus and stays there is associated with various cancers. But they didn't know what was keeping it active in the nucleus.

"Normally in the cell NF-kappa B is in the cytosol, it's not in the nucleus, and it's not activated," said University of Illinois medical biochemistry professor Lin-Feng Chen, who led the new study. "You have to stimulate normal cells to see NF-kappa B in the nucleus. But in cancer cells without any stimulation you can see this nuclear form of NF-kappa B. The cell just won't die because of this. That is why NF-kappa B is so important in cancer."

In the new study, Chen's group found that another molecule known to help regulate gene expression, called BRD4, recognizes a specific amino acid on a subunit of the NF-kappa B protein complex after the amino acid has been marked with a specific tag, called an acetyl group. This "acetylation" allows the BRD4 to bind to NF-kappa B, activating it and preventing its degradation in cancer cells.

Previous studies had shown that BRD4's recognition of the acetylated subunit increased NF-kappa B activation, but this recognition had not

been linked to cancer.

BRD4 belongs to a class of molecules that can recognize chemical markers on other proteins and interact with them to spur the marked proteins to perform new tasks. Chemical "readers" such as BRD4 are important players in the field of epigenetics, which focuses on how specific genes are regulated.

"In epigenetics, there are writers, there are readers and there are erasers," Chen said. The writers make modifications to proteins after they are formed, without changing the underlying sequence of the gene that codes for them. These modifications (such as acetylation) signal other molecules (the readers) to engage with the marked proteins in various ways, allowing the proteins to fulfill new roles in the life of the cell. Epigenetic erasers remove the marks when they are no longer of use.

Such protein modifications "have been shown to be critically involved in transcription regulation and cancer development," the researchers report.

To test whether BRD4 was contributing to the sustained presence of NF-kappa B in the nucleus of cancer cells, Chen and his colleagues exposed lung cancer cells in cell culture and in immune-deficient mice to JQ1, a drug that interferes with BRD4 activity. Exposure to JQ1 blocked the interaction of BRD4 and NF-kappa B, blocked the expression of genes regulated by NF-kappa B, reduced proliferation of lung cancer cells and suppressed the ability of lung cancer cells to induce tumors in immune-deficient mice, the researchers found.

The researchers also discovered that depletion of BRD4 or the treatment of cells with JQ1 induced the degradation of the NF-kappa B subunit recognized by BRD4.

Chen said that BRD4 likely prevents other molecules from recognizing the hyperactive NF-kappa B in the nucleus and marking it for degradation.

"This is an example of how epigenetic regulators and NF-kappa B may one day be targeted for the treatment of cancer," he said.

Researchers from Illinois biochemistry professor Satish Nair's laboratory and from the laboratory of James Bradner at the Dana-Farber Cancer Institute contributed to this study.

More information: "BRD4 Maintains Constitutively Active NF-κB in Cancer Cells by Binding to Acetylated RelA," *Oncogene*, 2013.

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