Overseers of cell death play wider role in protein quality control than believed, shows new study

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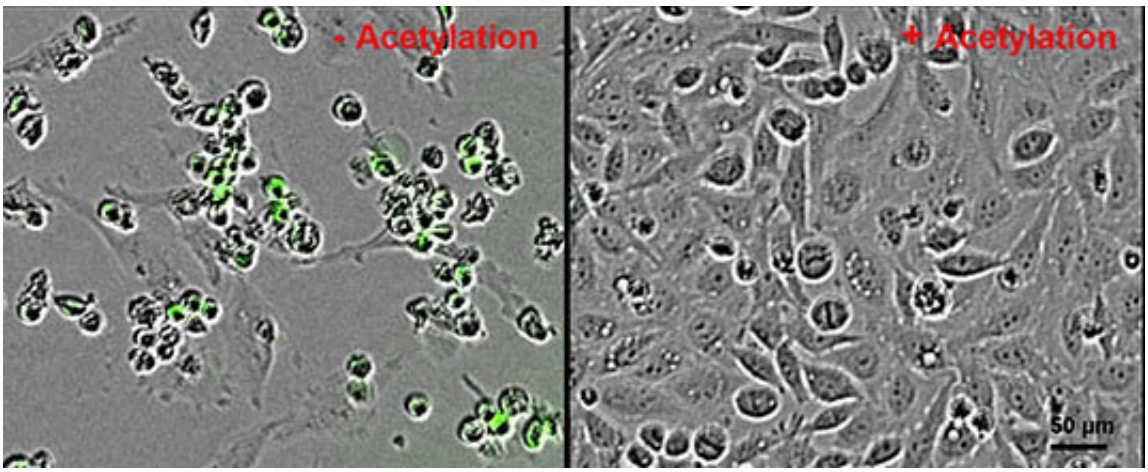

Cancer cells that lack the capacity for N-terminal acetylation (left) and control cells (right). Cells undergoing apoptosis are labeled in green. Credit: F. Mueller, T. Bange

A new study shows that proteins called IAPs, which can trigger programmed cell death, are inhibited by a specific chemical modification, and reveals that they play a wider role in protein quality control than previously assumed.

N-terminal acetylation—the attachment of an acetyl group ($CH_3^-COO^-$) directly to the N-terminus of a protein—is one of the most common modifications found in the protein complements of higher organisms.

The chemical tag has been linked to a wide variety of cellular signaling pathways. Now researchers led by Tanja Bange (Institute of Medical Psychology, LMU) have shown that N-terminal acetylation shields certain proteins from degradation, and inhibits programmed cell death ('apoptosis'). In their unacetylated state, these same proteins can induce apoptosis by interacting with proteins called IAPs. While the acronym refers to the function of IAPs as inhibitors of apoptosis, the new study suggests that they actually have a more general role in protein quality control. The work demonstrates for the first time that two fundamental cellular processes—N-terminal protein acetylation and programmed cell death—are functionally linked. This finding could open up new approaches to cancer therapy. The paper appears in the journal *Science Advances*.

As their name implies, IAPs are known to participate in the regulation of programmed cell death. They inhibit the process by binding to particular target proteins, and it was previously shown that IAPs can only do so as long as the N-termini of these targets are not acetylated. "In our experiments, we observed that a protein which is not involved in the control of apoptosis also binds exclusively to IAPs in its non-acetylated form," Bange explains. "This prompted us to explore the role of acetylation in the binding of proteins to IAPs in general."

In experiments on cultured cells, Bange and her colleagues were able to show that, as a general rule, IAPs indeed bind to proteins whose N-termini are unacetylated. It is also known that IAPs are able to induce their own destruction as well as the degradation of their binding partners. The authors therefore assume that IAPs have a hitherto unrecognized and general function in the quality control of newly synthesized proteins. "N-terminal acetylation protects proteins from degradation," says Bange. "If its N-terminus is not 'capped' in this way, a protein is recognized as defective by IAPs and destroyed. Conversely, if proteins that lack the modification accumulate in sufficient numbers, apoptosis is triggered."

These results could have therapeutic implications for the treatment of cancer. In many types of cancer, the signaling relays that trigger apoptosis are defective owing to mutation. This closes off one possible treatment option. According to the authors, inhibiting N-terminal acetylation pathways might provide a means of activating IAP function and sensitizing tumor cells to apoptosis.

More information: Franziska Mueller et al. Overlap of NatA and IAP substrates implicates N-terminal acetylation in protein stabilization, *Science Advances* (2021). DOI: 10.1126/sciadv.abc8590

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