ASK the enzyme: New potential targets for cancer

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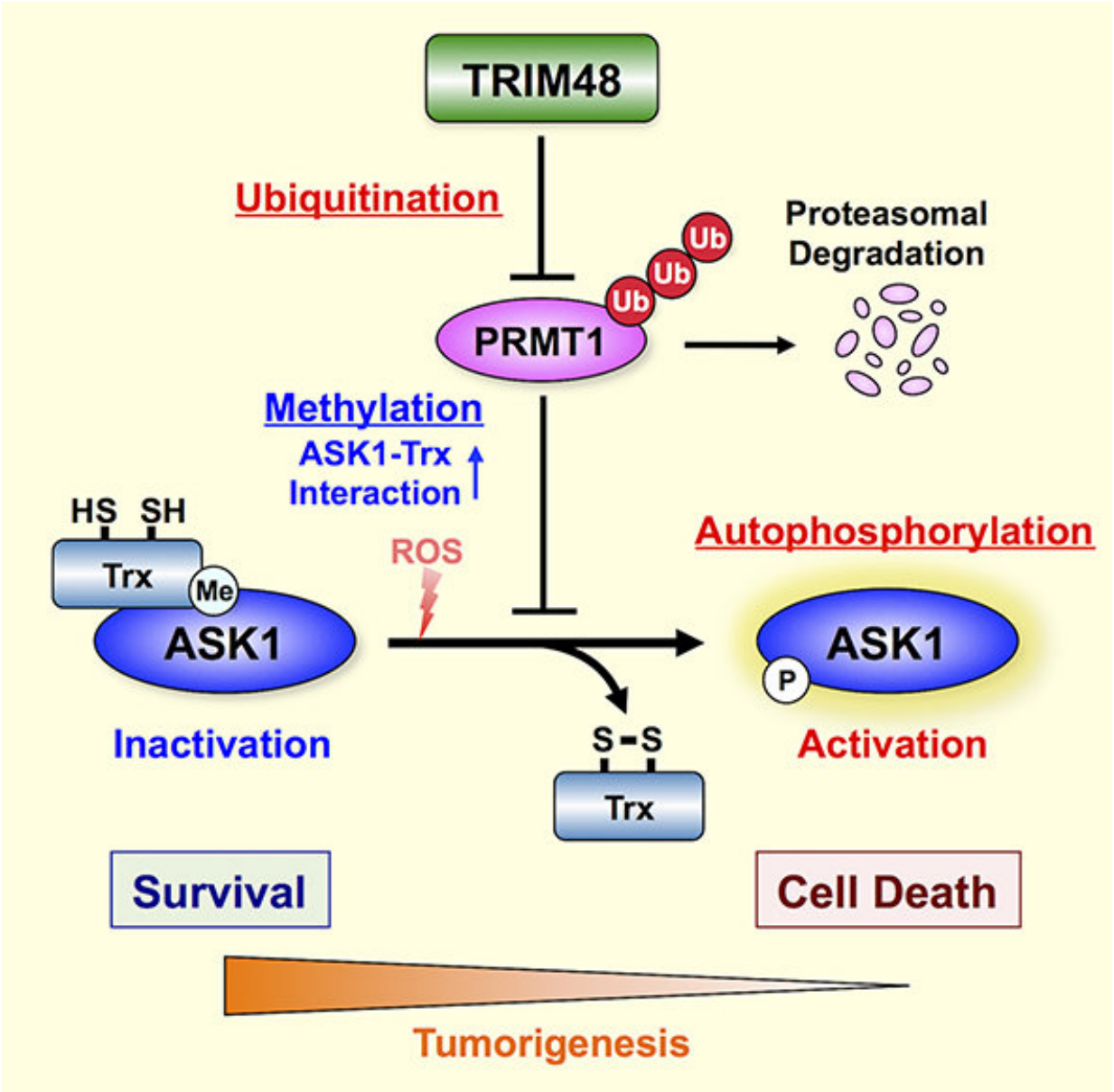

Tumor suppressive roles of TRIM48-mediated ASK1 activation and cell death. Credit: Atsushi Matsuzawa

New understandings of how molecules affect the activity of an enzyme could lead to potential targets for the treatment of cancers and neurodegenerative diseases.

Atsushi Matsuzawa at Tohoku University and colleagues in Japan used gene silencing techniques and cell culture studies to investigate how molecules regulate an enzyme known as apoptosis signal-regulating kinase 1 (ASK1). Irregular ASK1 activation is linked to some cancers, and inflammatory and neurodegenerative diseases.

ASK1 is normally activated in the body by oxidative stress, a process that involves high rates of oxygen metabolism and happens in response to stress, toxins and infections.

A variety of molecules are known to regulate ASK1, but how they do this has not been clear.

An enzyme called protein arginine methyltransferase 1 (PRMT1) is known to encourage ASK1 to interact with a small protein called thioredoxin (Trx). This interaction effectively turns ASK1 off, interfering with this enzyme's role in initiating a cell-signalling process that ultimately leads to cell death and inflammation.

Matsuzawa and his team found that a protein called tripartite motif 48 (TRIM48) starts a process that labels PRMT1 for destruction inside cells. PRMT1 deficiency means that ASK1 and Trx can't interact, which turns ASK1 on.

When the researchers turned off the gene that codes for TRIM48, ASK1 failed to be activated by oxidative stress.

When the researchers made the same gene work excessively in cancer cells planted under the skin in mice, they observed cancer cell death and suppression of tumour growth, possibly due to ASK1 hyperactivation.

"PRMT1 upregulation may be caused by decreased TRIM48 expression or activity, leading to cancer development and progression," write the researchers in their study published in the journal *Cell Reports*. "Future studies should determine whether TRIM48 suppresses cancer development and progression through PRMT1 downregulation," they say.

Further studies could reveal that the pathways involved in regulating ASK1 activation could act as therapeutic targets in the treatment of ASK1-related diseases, the researchers conclude.

More information: Yusuke Hirata et al, TRIM48 Promotes ASK1 Activation and Cell Death through Ubiquitination-Dependent Degradation of the ASK1-Negative Regulator PRMT1, *Cell Reports* (2017). DOI: 10.1016/j.celrep.2017.11.007

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