

RESEARCH WATCH

Imaging

Major finding: A topically applied, cancer cell-specific fluorescent probe visualizes ovarian tumors.

Concept: GGT on the surface of cancer cells rapidly activates the γ Glu-HMRG probe.

Impact: The γ Glu-HMRG probe can visualize cancer cells during surgical and endoscopic procedures.

A RAPIDLY ACTIVATABLE, TUMOR-SPECIFIC FLUORESCENT PROBE

The success of oncologic surgery depends on direct visualization and complete resection of both bulk tumor and local metastases. However, infiltrative tumor borders and tiny metastases may be difficult to discern with an unaided eye. Although the development of cancer-specific, fluorescent imaging probes has enhanced optically guided surgical and endoscopic procedures, existing antibody-based and enzyme-activatable probes can be slow to fluoresce and may require i.v. administration. Urano and colleagues developed a fluorescence-imaging probe that can be topically sprayed onto tumors and is rapidly activated by γ -glutamyltranspeptidase (GGT), a cell membrane-associated enzyme that is overexpressed in cervical and ovarian cancers. In its applied form, the γ -glutamyl methyl rhodamine green (γ Glu-HMRG) probe is inactive and hydrophilic. GGT on the surface of cancer cells hydrolyzes the probe, freeing the hydrophobic and highly fluorescent HMRG, which enters cancer cells and accumulates

in lysosomes. In this study, the probe was specifically activated by GGT-expressing ovarian cancer cells both *in vitro* and *in vivo*. Remarkably, when the probe was sprayed into the abdominal cavity of mice modeling invasive human ovarian cancer, tumor implants as small as 1 mm were visualized in as short a time as 10 seconds and remained fluorescent for at least 1 hour. With fluorescence-guided laparoscopy, the tumors were effectively removed. The advantages of the γ Glu-HMRG probe include its specificity, topical application, and rapidity of activation. Although use of the probe is limited to cancers that express GGT, its design could be applied to target additional cancer-specific cell surface enzymes. ■

Urano Y, Sakabe M, Kosaka N, Ogawa M, Mitsunaga M, Asanuma D, et al. Rapid cancer detection by topically spraying a γ -glutamyltranspeptidase-activated fluorescent probe. *Sci Transl Med* 2011;3:110ra119.

Metabolism

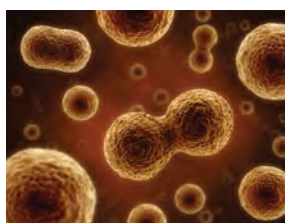
Major finding: AMPK substrate phosphorylation is required for completion of mitosis and cytokinesis.

Approach: An ATP analogue-specific AMPK α 2 mutant allows *in vivo* labeling of AMPK substrates.

Impact: Adipocytes secrete cytokines to attract tumor cells and provide lipids as an energy source.

AMPK COORDINATES NUTRIENT STATUS WITH CELL DIVISION

AMP-activated protein kinase (AMPK) is activated by cellular stimuli that increase the AMP:ATP ratio, such as low nutrient levels, and is a key regulator of energy homeostasis, although recent evidence has suggested that AMPK may function in other cellular processes. To systematically identify AMPK substrates and gain insight into the cellular function of AMPK, Banko and colleagues performed a chemical genetics screen for proteins directly phosphorylated by AMPK. Briefly, the ATP-binding pocket of one of the catalytic subunits of AMPK (AMPK α 2) was mutated such that it could accommodate bulky ATP analogues. These modified ATP nucleotides could then be transferred to AMPK α 2 substrates and be recognized by a specific monoclonal antibody. AMPK targets can thus be specifically labeled *in vivo*, immunoprecipitated, and analyzed by mass spectrometry. Using this approach, several known AMPK substrates were identified, along with 28 proteins not previously known to be targets of AMPK. These proteins were shown to be phosphorylated by endogenous AMPK in an *in vitro* kinase



assay, and AMPK phosphorylation consensus motifs were detected in many of these newly identified substrates. Unexpectedly, these substrates were significantly enriched for proteins involved in mitotic cell division. Consistent with a role of AMPK-dependent phosphorylation in mitosis, AMPK activity, as well as phosphorylation of the newly identified AMPK substrate, PPP1R12C, was increased in mitotic cells. Furthermore, AMPK inhibition and mutation of the AMPK phosphorylation site in PPP1R12C similarly impaired the completion of cell division, as evidenced by an increase in multinucleated cells. These findings provide a mechanism for AMPK activity in mitosis and raise the intriguing possibility that the suspected tumor suppressor function of AMPK may be linked to its ability to coordinate mitotic progression with cellular energy status. ■

Banko MR, Allen JJ, Schaffer BE, Wilker EW, Tsou P, White JL, et al. Chemical genetic screen for AMPK α 2 substrates uncovers a network of proteins involved in mitosis. *Mol Cell* 2012;45:1–15.

CANCER DISCOVERY

AMPK Coordinates Nutrient Status with Cell Division

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