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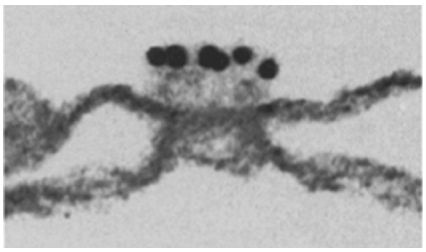
Text by Ben Short
bshort@rockefeller.edu

SUMO enters the ring

In 1996, Matunis et al. were one of several groups to identify a novel, ubiquitin-like protein modification.



Immunogold electron microscopy shows that the SUMOylated, 90-kD form of RanGAP1 (black dots) localizes to the tips of fibers emanating from the cytoplasmic face of the nuclear pore complex.

By the mid-1990s, it was clear that conjugation to ubiquitin could affect not just a protein's stability, but also its localization and activity. Whether there were other proteins in the cell that could also be covalently linked to substrates in order to regulate their function was unknown, at least until Matunis et al. (1), along with several other groups (2–6), identified the protein that would come to be known as small ubiquitin-like modifier, or SUMO.

Mike Matunis didn't set out to discover new, ubiquitin-like proteins. Rather, when he started his postdoc with Günter Blobel at The Rockefeller University in New York, Matunis was interested in following up on recent reports linking the Ran GTPase to nucleocytoplasmic transport (7, 8). "Ran seemed to be acting at the nuclear pore," explains Matunis, now at Johns Hopkins University in Baltimore. "There was this idea that Ran was binding to the pore to open it or facilitate transport in some way, so we wanted to identify nuclear pore proteins that bound to Ran."

> "When I saw the band... I knew what we were working with."

Together with another postdoc, Elias Coutavas, Matunis found that active, GTP-bound Ran associated with a 90-kD protein found in isolated nuclear membranes (1). Partial sequencing of this protein revealed that it was largely identical to RanGAP1, a GTPase-activating protein that stimulates Ran's ability to hydrolyze GTP. RanGAP1, however, was known to have a molecular weight of ~70 kD. The 90-kD Ran-binding protein in nuclear membranes contained an additional peptide sequence that corresponded to an uncharacterized human cDNA fragment, clone 32220.

"This was before the genome was sequenced, so, at first, we thought the 90-kD protein must be an alternatively spliced version of RanGAP1," Matunis recalls. "For six months or more we screened libraries for an mRNA encoding the entire protein, without any success."

An alternative explanation was that the 90-KD protein was a posttranslationally modified version of RanGAP1. Clone 32220 was 18% identical to ubiquitin, but the idea that it might encode a ubiquitin-like protein that could be conjugated to RanGAP1 seemed far-fetched. "Ubiquitin is 100% conserved between yeast and humans, so it wasn't clear that something that was only 18% conserved could be a ubiquitin-like protein," Matunis explains. But Erica Johnson, who had studied ubiquitin as a student with Alex Varshavsky and was now also a postdoc in the Blobel lab, persisted in pushing the idea.

Matunis' perception changed when he raised a monoclonal antibody against the protein encoded by clone 32220. This antibody recognized the 90-kD Ran-binding protein in isolated nuclear membranes, as did an anti-RanGAP1 antibody. Crucially, however, when nuclear membrane fractions were treated with a particular ionic detergent, the 90-kD protein disappeared. Anti-RanGAP1 now recognized a 70-kD protein in western blots, while Matunis' new antibody now detected a 15-kD protein, indicating that—just like ubiquitin—the small protein encoded by clone 32220 could be reversibly linked to other proteins, such as RanGAP1. "I can still remember developing the autorad in the darkroom," Matunis says. "When I saw the band go from 90 to 15 kD, I knew what we were working with."

Matunis named the ubiquitin-like protein GAP modifying protein 1, or GMP1. Around the same time, however, several other groups discovered the same protein, each giving it their own name (2–6). Mahajan et al., who also discovered the protein as a small, ubiquitin-like modifier of RanGAP1, gave it the catchy name SUMO (6). "I knew immediately that that name was going to stick," Matunis laughs.

Matunis subsequently found that SUMOylation helps target RanGAP1 to the nuclear pore complex (9). "But the functional significance of this is still not known," Matunis says. As he set up his own lab at Johns Hopkins, he was more interested in what else SUMO might be doing, having seen, using his anti-GMP1 antibody, that SUMO could be conjugated to plenty of other proteins in the cell.

"We now know that several thousand proteins can be conjugated to SUMO, but only a tiny fraction of each protein is SUMOylated at steady state," Matunis says. "What's the significance of this? One idea is that SUMO has a sort of chaperone function, helping proteins to fold or avoid aggregation."

"The discovery of the SUMO system and the subsequent identification of its cellular targets dramatically changed our view on central cellular processes, such as DNA repair or gene regulation," says Ivan Dikic, a *JCB* academic editor and an expert on ubiquitin and ubiquitin-like modifiers. "This early discovery by Michael and others has expanded toward a broader biomedical importance. It has been established that changes in the SUMO pathway can result in development of human diseases including cancer. Reflecting this importance, novel inhibitors of SUMO ligases will soon enter clinical trials for anticancer treatments."

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