fortes of both inorganic semiconductors (ease of light generation) and organic semiconductors (flexibility in the wavelength generated). First, a high-power inorganic LED — unconventionally operated in a pulsed mode with its focusing lens removed — generates incoherent, spectrally broad light. That light is then converted into coherent radiation in an organic, plastic lasing medium situated immediately beneath the LED (Fig. 1a). For this medium, the authors chose a conjugated polymer derived from polyfluorene, with a backbone consisting of paired phenylene rings (Fig. 1b). The characteristic alternation of single and double covalent (shared-electron) bonds in this hydrocarbon chain means electrons can move along it efficiently, such that its response to the optical pumping from the LED is strong.

The new device is more compact and much cheaper than plastic lasers pumped with inorganic laser diodes[7,8]. Whereas such diodes emitting blue or ultraviolet light come with price tags of hundreds of dollars, high-power LEDs (which are also increasingly edging out traditional incandescent bulbs for lighting applications) are available for just cents. But that's not the best of it: because plastics are inherently disordered, made up of polymer chains jumbled up like a plate of spaghetti, different units on a chain emit light of slightly different colours. The absorption spectrum of the whole ensemble is made up of a superposition of narrower transitions corresponding to these units (Fig. 1c). Whereas a narrow-band pump laser will excite only a small subset of the molecules available, an LED with a broad emission spectrum can shovel more optically active units into the excited state, potentially lowering the threshold power needed to stimulate lasing.

By changing the laser medium and varying the corrugation of the silica substrate on which the device rests, it will be easy to tune such a laser system across the visible spectrum[9]. Plastics are not good conductors of heat, and so plastic lasers are unlikely to provide high power output, but in many applications — biomedical diagnostics and optical communications[10], to name but two areas — precise wavelength control trumps brute force. The lasing future of plastics might not be as bright as that of other materials; but it certainly promises to be more colourful. ■

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CELL BIOLOGY

Two hands for degradation

Yasushi Saeki and Keiji Tanaka

Living cells must do away with regulatory proteins that are not needed. News comes of a considerable advance in understanding how the main agent of destruction, the proteasome, catches its targets.

The 26S proteasome is a formidable piece of equipment — it is one of the principal cellular machines for carrying out the essential task of degrading proteins. Proteins to be destroyed are marked with tags in the form of the small protein ubiquitin, and when the proteasome encounters such polyubiquitinated proteins, it catches, then degrades them. Papers by Husnjak *et al.*[1] and Schreiner *et al.*[2], which are the fruits of a multi-group collaboration and appear on pages 481 and 548 of this issue, show that the proteasome has, not one, but at least two hands with which it latches on to its ubiquitinated prey.

The ubiquitin–proteasome system controls almost all cellular processes — such as progression through the cell-division cycle and signal transduction — by degrading regulatory proteins[3]. The long journey to the destruction of a protein is started by covalent tagging with a chain consisting of several copies of ubiquitin, through the concerted action of a cascade of enzymes. Principally, polyubiquitin chains that consist of up to four or more ubiquitin molecules serve to promote degradation by the 26S proteasome. This protein is a multi-catalytic enzyme, with a highly ordered structure that is composed of at least 33 different subunits arranged in two sub-complexes — a 20S core particle and one or two 19S regulatory particles. The protein-degrading sites lie inside the core particle and are accessible only through a narrow channel, so substrate proteins must be unfolded to reach the sites. The regulatory particle recognizes the polyubiquitin chains and removes them, then unfolds the substrate proteins and transfers them into the core particle for destruction.

How the polyubiquitinated proteins are recognized by the proteasome is a fundamental and long-standing question. In 1994, Rpn10, one subunit of the regulatory particles, was identified as a protein that binds to polyubiquitin chains; it does so via a ubiquitin-interacting motif (UIM) found at one end of the protein (the carboxy terminus)[4,5]. Genetic experiments in yeast, however, showed that deletion of the *RPN10* gene or a *uim* mutation had few or no effects. These results raised the possibility that other proteasomal ubiquitin receptors exist that can compensate for Rpn10 function.

Several laboratories pursued this possibility and identified proteins with particular structural units — ubiquitin-like proteasome-binding domains (UBL) and ubiquitin-associated domains (UBA) — as being implicated in targeting ubiquitin. The proteins concerned included Rad23, Dsk2 and Ddi1 (refs 5, 6). The finding that *RAD23* and *DSK2* interact genetically with the *rpn10* mutation, together with a subsequent biochemical study, established that the UBL–UBA-containing proteins function

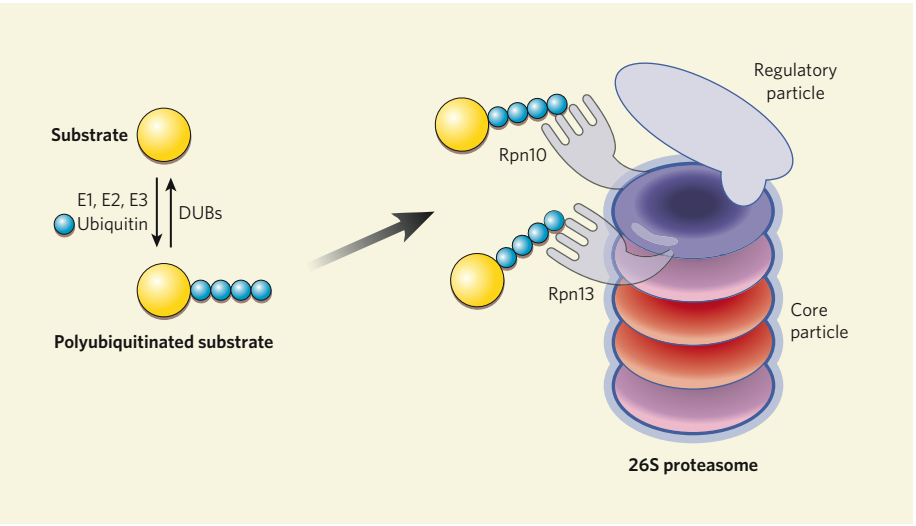

Figure 1 | A pair of hands for catching ubiquitin. Protein substrates are marked for degradation by polyubiquitination, which is carried out by E1 (activating), E2 (conjugating) and E3 (ligating) enzymes; deubiquitinating enzymes (DUBs) can reverse this process. If it is not reversed, the ubiquitin units are recognized by the 26S proteasome protein-degrading machine through two intrinsic receptors, Rpn10 and the newly identified[1,2] Rpn13. Extrinsic ubiquitin receptors, such as Rad23, Dsk2 and Ddi1 (not shown), also function cooperatively in this process.

as extrinsic ubiquitin receptors of the proteasome[5,7]. Thus, the question of ubiquitin receptors seemed to be answered. As we now find out, however, the 26S proteasome concealed an additional intrinsic ubiquitin receptor.

In the first of the new papers, Husnjak *et al.*[1] describe how they have identified human Rpn13, a regulatory-particle subunit, as a ubiquitin-binding protein. Although both the amino- and carboxy-terminal regions of Rpn13 are conserved among species, the ubiquitin-binding activity is located at what is known as a pleckstrin-homology-like domain at the amino terminus (pleckstrin-homology domains are common in proteins involved in intracellular signalling). Rpn13 from budding yeast has only the amino-terminal conserved domain.

Husnjak *et al.*[1] first addressed the significance of the ubiquitin-binding activity of Rpn13 in purified 26S proteasomes. Although proteasomes lacking all known ubiquitin-receptor activities — including the UIM of Rpn10 and three UBL–UBA-containing proteins — still bound to the polyubiquitinated substrate, additional deletion of Rpn13 resulted in almost total loss of ubiquitin-binding activity. The defect was restored by either Rpn10 or Rpn13. These results clearly suggest that Rpn10 and Rpn13 are the primary ubiquitin receptors of the 26S proteasome (Fig. 1).

The amino-terminal domain of Rpn13 shows no similarity to known ubiquitin-binding motifs. As Husnjak *et al.*[1] and Schreiner *et al.*[2] recount, the next phase of the research was to use nuclear magnetic resonance and crystallographic studies to determine how Rpn13 binds ubiquitin. These structural analyses revealed that the amino-terminal domain has a canonical pleckstrin-homology fold consisting, in technical terms, of a seven-stranded β-sandwich structure capped by the carboxy-terminal α-helix. The authors therefore named this domain 'pleckstrin-like receptor for ubiquitin' (Pru).

They found that the Pru domain of human Rpn13 shows high affinity (around 90 nanomolar) for diubiquitin, the strongest binding among the known ubiquitin receptors. Both human and yeast Rpn13 Pru domains use three loops at one edge of their β-sheet to bind ubiquitin. The authors successfully created an *rpn13* mutant (called *rpn13–KKD*) that lost ubiquitin-binding capacity without compromising proteasome integrity, and tested the biological effects of this mutation in yeast. Degradation of a model substrate protein of the ubiquitin–proteasome system was retarded in this mutant; and when combined with an *rpn10–uim* mutant, the cells showed further impairment of proteasome function. In addition, polyubiquitinated proteins accumulated in the *rpn10–uim, rpn13–KKD* mutant cells. These results suggest that Rpn13 is a true intrinsic ubiquitin receptor of the 26S proteasome, and that it collaborates with Rpn10 *in vivo*.

An obvious question that arises is why there are so many ubiquitin receptors in the ubiquitin–proteasome system. The 26S proteasome binds with high affinity to the longer polyubiquitin chains, so it is likely that both Rpn13 and Rpn10 can bind simultaneously to a substrate that bears such chains. Rpn13 Pru can also recognize UBL–UBA-containing proteins[1,2], as mammalian Rpn10 does[4]. Perhaps polyubiquitin recognition at multiple sites in the proteasome enhances targeting potency and stabilizes the proteasome–substrate complex for substrate degradation. Intriguingly, yeast cells with mutations in five ubiquitin receptors are still viable, indicating that there may still be unidentified ubiquitin receptors in the proteasome, perhaps operating downstream from Rpn10 and Rpn13. In mammalian cells, Rpn13 binds via its carboxy-terminal domain to Uch37, one of three proteasome-associated deubiquitinating enzymes[8–10]. This means that Rpn13 might be a specialized ubiquitin receptor that can fine-tune the timing of substrate degradation.

More generally, it is becoming apparent that there are several layers to proteasome regulation, and that this may allow the proteasome to cope with high substrate flux as well as a wide diversity of substrates. The identification of Rpn13 as a ubiquitin receptor will help in directing research to elucidate these intricate mechanisms. ■

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BIOPHYSICS

Cells get in shape for a crawl

Jason M. Haugh

A cell's shape changes as it moves along a surface. The forward-thinking cytoskeletal elements are all for progress, but the conservative cell membrane keeps them under control by physically opposing their movement.

The ability of living cells to move affects the way our bodies develop, fight off infections and heal wounds. Moreover, cell migration is an extremely complex process, which explains why it has captured the collective imaginations of a variety of fields, from the biological and the physical sciences. This is good news, because cell motility is determined in equal parts by biochemistry and mechanics[1,2], and so understanding and manipulating it require the sort of clever approach that comes only from the integration of multiple scientific disciplines. On page 475 of this issue, Keren *et al.*[3] combine approaches familiar to cell biology with those familiar to applied mathematics and physics to address how the forces generated by specific molecular processes in a cell produce its observed shape.

The starting point for the authors' analysis was the characterization of variability in the shapes adopted by epithelial keratocytes from fish skin in culture. These cells serve as a unique model system for studying cell migration, because they crawl rapidly and without frequent changes in direction, and maintain a nearly constant shape as they move. Their stereotypical shape, often described as an 'inverted canoe', is characterized by a broad membrane structure at its front, the lamellipodium, which protrudes forward in concert with forces that act at the rear of the cell. The authors determined that most of the shape variability could be attributed to differences in cell size and, to a lesser extent, the aspect ratio of its characteristic dimensions (the ratio of its width to its height).

The key insight by Keren *et al.* was to relate two independent observations: the cell's shape and its distribution of actin filaments. Actin filaments are structural elements inside the cell that, through the energy-intensive process of adding (and later removing) protein subunits, produce the mechanical work required to push the cell forward. New, growing filaments are formed by the branching off of existing ones, a process that is well understood in keratocytes[4,5].

Building on previous work[6], the authors propose a mathematical model to explain the observation that the filament density at the cell front is graded, with the highest density at its centre (Fig. 1). The importance of this approach is that it incorporates known molecular mechanisms, and hence the model could be used to predict what might happen if the functions of the molecules involved were perturbed. The authors next invoked what is known as the force–velocity relationship, which states that the rate at which the