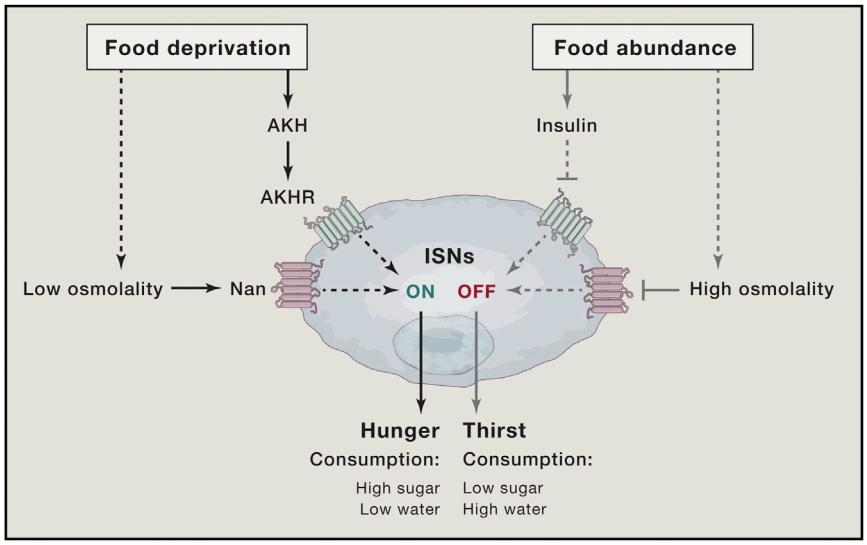

Figure 1. Integration of Nutrient Signals by ISNs for Homeostatic Regulation of Feeding and Drinking

The hunger signal AKH and low osmolality detected by the Nan channel activate ISNs, leading to high sugar and low water consumption. Opposing signals such as insulin and high osmolality instead limit firing of ISNs, causing lower sugar and higher water consumption.

Further, the ghrelin peptide has been found to regulate food consumption and, in some thirst-inducing conditions, water intake (Mietlicki et al., 2009).

The neuronal networks that integrate internal nutrient abundance signals and couple them to homeostatic behaviors remain largely unexplored, and yet disruption of this machinery could potentially contribute to the onset of homeostatic disorders like obesity-linked diabetes. Hence, the work of Jourjine et al. (2016) provides an excellent stepping stone for future research in this direction.

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Look Out Autophagy, Ubiquilin UPS Its Game

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Mutations in Ubiquilin-2 are linked to the onset of amyotrophic lateral sclerosis, but its connection to disease processes has remained unknown. Hjerpe et. al now report that Ubiquilin-2 enables the ubiquitin proteasome system (UPS) to single-handedly clear aggregated proteins, a cellular function previously thought to rely at least partially on autophagy.

Amyotrophic lateral sclerosis (ALS) is a rapidly progressing neurological disease caused by motor-neuron degeneration in the brain and spinal cord, leading to paralysis and death typically within 2–5 years of onset. As with many other neurodegenerative diseases, the remarkable complexity of ALS etiology has historically stifled all attempts at a mechanistic understanding of ALS, let alone therapeutic design. Recent years, however, have seen a seismic shift in the appreciation of the molecular underpinnings of the disease, mainly thanks to systematic sequencing of patient genomes, combined with new cell biological insight (Chesi et al., 2013). As it is currently understood, most cases of ALS are pathologically related to a cell biological feature, namely neuronal aggregates of TDP-43, an RNA-binding protein. These aggregates, in turn, can often be traced to genetic mutations in TDP-43 or functionally related RNA-binding proteins,

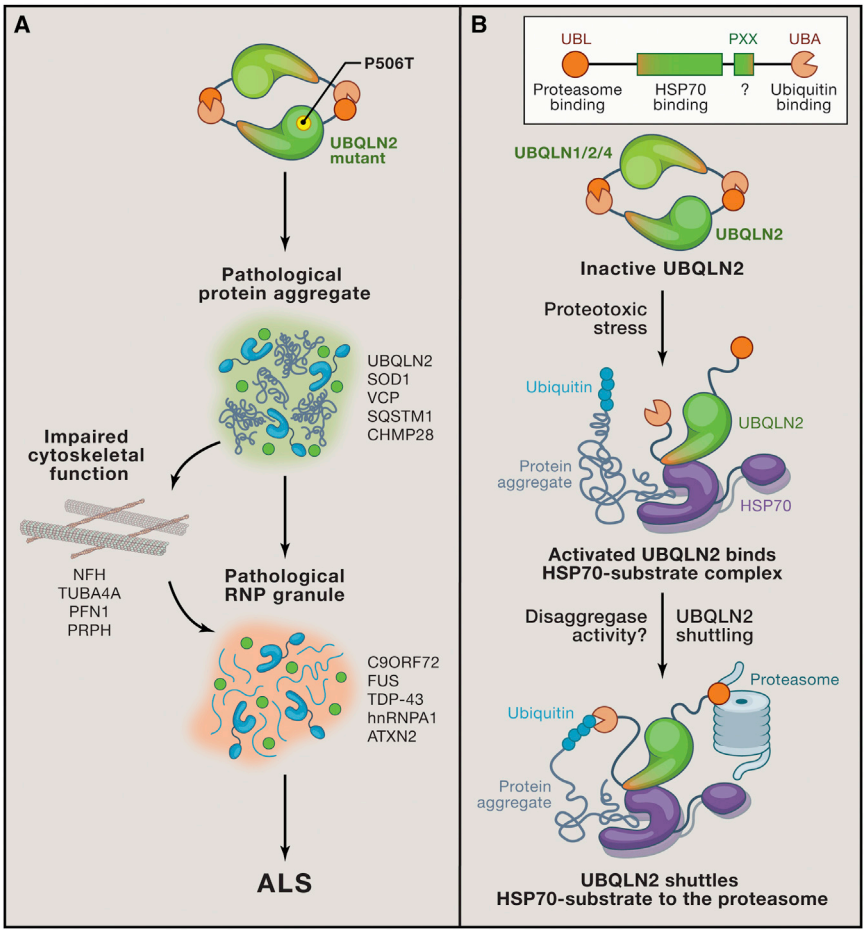

Figure 1. UBQLN2 Shuttles Substrate-Bound Hsp70 to the Proteasome for Degradation

(A) Most ALS-related genes can be categorized into one of three groups: those that affect RNA metabolism, those that affect proteostasis, and those that impair cytoskeletal function. However, an underlying mechanistic relationship is beginning to emerge between these groups. While UBQLN2 mutations directly result in pathological protein aggregation, they may also indirectly promote cytoskeleton dysfunction and impaired RNA metabolism, resulting in ALS onset.

(B) Under non-stress conditions, UBQLN2 associates with other UBQLNs (UBQLN1, UBQLN2, and UBQLN4), and is held inactive. Upon proteotoxic stress UBQLN2 is activated and binds to substrate-bound Hsp70. Ubiquination is not required for UBQLN2 binding. UBQLN2 then shuttles this complex to the proteasome for degradation. UBA, Ubiquitin associating domain, PXX, proline repeat motif, UBL, Ubiquitin-like domain.

predominantly the protein FUS. In fact, an increasing fraction of ALS cases, including those absent a family history of the disease, have been shown to have a genetic component in the RNA processing pathway as well as in other pathways that, at first glance, appear unrelated. Most ALS-related genes can be categorized into one of three groups: those that affect RNA metabolism and transport (such as FUS, TDP-43, and C9orf72), those that affect proteostasis (such as SOD1, VCP, and SQSTM1), and those that impair cytoskeletal transport (such as NFH, PFN1, and TUBA4A) (Peters et al., 2015). Intriguingly, an underlying mechanistic relationship between these mutations is beginning to emerge (Figure 1A). For example, RNA-binding proteins are thought to function in phase-separated liquid-like dynamic droplets or RNA-protein (RNP) granules (Zhang et al., 2015; Amen and Kaganovich, 2015), which require a robust proteostasis environment to remain soluble and functional due to the high prevalence of disordered and glutamine-rich regions in their sequences. RNP granule function may therefore be the first casualty of high-misfolded protein concentrations in the cytoplasm, as well as the titration of protein folding resources by aggregates.

In this issue of *Cell*, Hjerpe et al. (2016) find a surprising new role in modulating proteostasis for a gene, Ubiquilin-2 (UBQLN2), that has recently been implicated in ALS (Deng et al., 2011). UBQLN2 is a member of a protein shuttling family containing an N-terminal ubiquitin-like (UBL) domain, which interacts with the proteasome, and a C-terminal ubiquitin-associated (UBA) domain that binds polyubiquinated proteins (Figure 1B). There are a number of such shuttle proteins including Ddi1, Rad23/hHR23 and UBQLN/hPLIC/Dsk2. Dsk2 (the yeast homolog of UBQLN) has long stood out as the only shuttle protein that is toxic at high levels (Matiuhin et al., 2008). Another unique feature of UBQLN/Dsk2 is a middle region containing STI1-like repeats that bind Stch, an Hsp70-like chaperone (Kaye et al., 2000). Interestingly, most of the known UBQLN2 ALS mutations are associated with a proline repeat motif (Pxx) within this central domain.

Hjerpe et al. first demonstrate that UBQLN2 plays a direct role in facilitating the clearance of polyubiquinated protein aggregates after proteotoxic stress. Though previous findings had implicated UBQLN2 disease-linked mutations in aggregate formation, the mechanism of aggregate clearance was uncertain. Hjerpe et al. (2016) found that the central domain of UBQLN2 interacts with HSP70, and that in concert with the HSP70-HSP110 disaggregase machinery, UBQLN2 mediates the proteasomal degradation of protein aggregates.

In order to gain further insight into the mechanism of UBQLN2-mediated aggregate clearance, the authors examined the interactome of wild-type and mutant UBQLN2. They found that, under non-stress conditions, UBQLN2 is soluble, and primarily associates with other ubiquilins (UBQLN1,2,4). Then, upon proteaotoxic stress, UBQLN2 selectively binds to substrate-bound HSP70, shuttling it to the proteasome (Figure 1B). Strikingly, disease-linked mutations in UBQLN2 abolish the stress-induced interaction with Hsp70.

In another important finding, the authors demonstrate that UBQLN2-mediated proteolysis of aggregation-prone proteins appears to take place solely via the 26S proteasome. Whereas proteasome inhibition prevents aggregate clearance, autophagy-deficient (atg5 knockout) cells are capable of clearing aggregates as efficiently as wild-type cells. These results are surprising, given that the proteasome contains a narrow (~1.5 nm) entrance to its proteolytic chamber necessitating the complete unfolding of any substrate, whereas aggregated proteins are notoriously difficult to unfold. Though it has been widely hypothesized that protein aggregates require autophagy for degradation, Hjerpe et al. nevertheless suggest that, at least in the case of certain stress induced aggregates, the 26S proteasome is sufficient when UBQLN2 is around. These results also imply that UBQLN2-mediated aggregate clearance is coupled to disaggregase activity. The issue of whether human cells are capable of disaggregating large protein aggregates has also been controversial due to the fact that mammals do not possess an Hsp104 disaggregase homolog. On the other hand, it was recently demonstrated that the Hsp70-J-protein-Hsp110 chaperone network can provide potent protein disaggregation activity in mammalian cells (Nillegoda et al., 2015). It will be valuable to examine in future studies whether the disaggregase activity supplied by Hsp70-Hsp110 is sufficiently robust to process most protein aggregates or whether the titration of monomers via degradation shifts the balance between partially soluble and aggregated misfolded proteins.

Finally, the authors utilize a mouse expressing glutamine-expanded Huntingtin as a model for aggregation, showing that UBQLN2 associates with aggregated polyQ Huntingtin. Mutating UBQLN2 in this background results in cognitive deficits and increased polyQ Huntingtin aggregation. Interestingly, it has been demonstrated that UBQLN2 only binds to particular types of protein aggregates: whereas UBQLN2 associates strongly with Huntingtin, it does not so with aggregates of ATXN3, Synuclein, or Tau (Zeng et al., 2015). Moving forward, it will be essential to ascertain which specific features target an aggregate for UBQLN2-mediated degradation, and to examine the possibility that by interfering with aggregate clearance, UBQLN2 mutants exert a secondary effect on TDP43 and FUS in RNP granules, thus triggering the familiar ALS cellular pathology.

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Kidney Macrophages: Unique Position Solves a Complex Problem

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Immune complex-mediated diseases, such as systemic lupus erythematosus, commonly affect the kidney and determine disease prognosis. Stamatiades et al. now propose a kidney-specific mechanism for trans-endothelial transport of small immune complexes that activate strategically positioned tissue resident macrophages.

IgG antibodies are the key soluble effector molecules of the adaptive immune system. Upon IgG binding to antigen, immune complexes (IC) are formed, allowing the engagement of powerful effector mechanisms, including Fcγ receptor (FcγR) ligation and complement activation. This process ensures effective antimicrobial activity. However, if circulating IC are not adequately cleared by macrophages of the reticuloendothelial system (RES) in the liver and spleen,