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Saved by the Matrix: UPR Independent Survival under ER Stress

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Cells are protected from endoplasmic reticulum stress through the unfolded protein response (UPR). In this issue of *Cell*, Schinzel, Higuchi-Sanabria, Shalem et al., identify a mechanism that helps cells cope with ER stress but is independent of canonical UPR activation, instead involving the extracellular matrix hyaluronidase, TMEM2, as a signaling mediator.

Aging is a major risk factor for most chronic diseases affecting the human population, which include diabetes, neurodegeneration, and immune diseases. A hampered ability of cells to cope with cellular damage contributes to this decline. Boosting cellular mechanisms that ameliorate age-related damage or its cellular consequences could therefore, as a strategy, extend healthspan (Kennedy et al., 2014).

The endoplasmic reticulum (ER) is responsible for the folding of proteins in the secretory pathway, which constitutes about 30% of the proteome. In young and healthy cells, the ER is remarkably plastic and able to respond to excess misfolded proteins through a set of adaptive stress response pathways, collectively called the unfolded protein response (UPR) (Martínez et al., 2017). The UPR is initiated by the activity of three sensors, protein kinase RNA-like ER kinase (PERK), inositol-requiring protein 1 α (IRE1α), and activating transcription factor 6 (ATF6). Together, they activate pathways that, among others, block general protein synthesis and reinforce ER-specific molecular chaperones, quality control mechanisms, and protein degradation pathways (ERAD and autophagy) (Figure 1A) to restore ER homeostasis (Hetz, 2012). In the case of irreparable damage, the UPR enters a terminal response, which leads to the removal of cells by apoptosis (Figure 1B).

In aging cells, the adaptive response becomes increasingly compromised, which shifts the balance toward a loss of cell physiology due to the impaired production of secretory pathway cargoes that have central functions (Balch et al., 2008). However, the mechanisms that determine cell fate under ER stress are still poorly understood. Here, Schinzel and colleagues performed an unbiased screen to identify central regulators of cell survival under ER stress. They discover TMEM2, an extracellular matrix enzyme, as a protective factor that signals through the MAPK pathway independent of the UPR (Figure 1B). Remarkably, modulation of the same cascade in the nematode *C. elegans* by expression of the human TMEM2 also enhances ER stress resistance and, moreover, prolongs lifespan by suppressing immunosenescence, suggesting an evolutionarily conserved protective function.

The mechanisms that govern activation of ER stress-dependent apoptosis are complex and do not depend on a single signaling pathway. So far, it is clear that, under irreversible ER stress, signals emerge from terminal UPR converge into the core mitochondrial pathway controlled by the BCL-2 family, leading to caspase activation. Other components accelerate cell death when ER proteostasis is impaired, including sterile inflammation, control of microRNA and mRNA stability, and the expression of CHOP, which enhances ROS production and protein synthesis in the stressed cell, resulting in proteotoxicity (Wang and Kaufman 2016) (Figure 1B). Early studies suggested that IRE1α, the most conserved UPR stress sensor, also acts as a scaffold for adaptor proteins, which engages the MAP kinase. This signaling crosstalk may contribute to the activation of prosurvival autophagy or apoptosis under ER stress (Hetz 2012).

Transmembrane protein 2 (TMEM2) has recently been discovered as the missing extracellular hyaluronidase in the turnover of the glucosaminoglycan, Hyaluronan (HA) (Yamaguchi et al., 2019). HA is an extremely long polymer of repeating disacharides (sometimes reaching 10^7 Da) that has a high turnover rate. HA represents a major component of the extracellular matrix that provides compression strength and hydration within the extracellular matrix (ECM), in addition to regulating cellular processes such as adhesion, motility, proliferation, and differentiation (Cyphert et al., 2015). TMEM2 is responsible for the degradation of HA into intermediately sized fragments (10–100 kDa), which occurs outside of the cell. Further processing into smaller fragments occurs inside the cell by lysosomal hyaluronidases and exoglucosidases (Yamaguchi et al., 2019). Proper HA turnover is important for health, because genetic mutations in hyaluronidases have been shown to cause developmental defects and disease. For example, a mutation of TMEM2 in zebrafish impairs endocardial cushion development and a defect in hyaluronidase 1 causes a lysosomal storage disease (Yamaguchi et al., 2019). The cleavage products also play a critical role in these processes (Cyphert et al., 2015). The low-molecular-weight

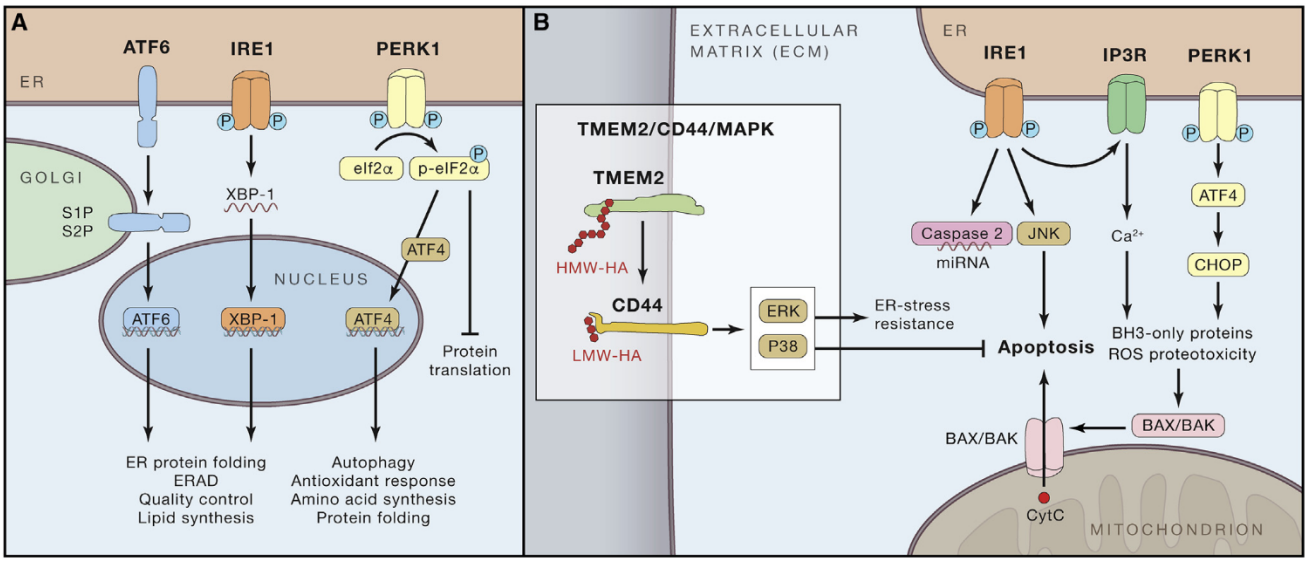

Figure 1. UPR-Independent Protection against ER Stress

(A) The adaptive UPR comprises three canonical branches: ATF6, IRE1-XBP-1, and the PERK-eIF2α pathway. These three branches, among others, block protein translation, reinforce ER-specific molecular chaperones, and induce several protein degradation pathways. The activation of the UPR aims to restore ER homeostasis.

(B) In the case of irreparable damage or sustained activation of the UPR branches, that pathway shifts toward pro-apoptotic signaling. The exact mechanisms that underlie this shift in cell fate are unclear, but a role for ATF4-CHOP and JNK signaling is described. Schinzel et al. describe an extracellular-matrix-associated pathway that influences ER stress resistance independent of the canonical UPR. Breakdown of high-molecular-weight (HMW)-HA in the extracellular matrix by TMEM2 is followed by the activation of CD44 by low-molecular-weight (LMW)-HA. Activation of the CD44 receptor engages ERK and P38 (components of the MAPK pathway), which results in cells being more viable under stress.

fragments, for example, have been shown to activate cellular receptors that engage signaling cascades to sustain cellular fitness. Both systemic and cell-autonomous consequence of the TMEM2 signaling pathway contribute to organismal health.

In this issue of *Cell*, using a whole-genome CRISPR knockout screen in human fibroblasts, Schinzel, Higuchi-Sanabria, Shalem, et al. identified TMEM2 as a modulator of ER stress resistance (Schinzel et al., 2019). Genetic and chemical inhibition of components of the canonical UPR components suggested that TMEM2 may act independently of these pathways. They provide data indicating that breakdown of HA increases ER stress resistance. Mechanistically, low-molecular-weight fragments of HA molecules appear to activate the CD44 receptor, which then engages the MAPK pathway components ERK and p38 to keep the cells viable under stress (Figure 1B).

Since ER stress has been linked to lifespan control in *C. elegans* (Taylor and Dillin, 2013; Henis-Korenblit et al., 2010), the authors use this model to enforce the expression of human TMEM2 and determine its impact in aging. TMEM2 expression extended lifespan by improving pathogen resistance. Similar to the phenotypes found in human cells, lifespan extension is independent of the canonical ER stress response pathway and dependent on the *C. elegans* orthologs of ERK and p38.

Why does TMEM2, as a regulator of extracellular matrix homeostasis, modulate ER stress resistance? Although the authors provide some evidence suggesting that the protection against cell death by TMEM2 is UPR independent, it is possible that ER proteostasis alterations result in TMEM2/CD44/MAPK signaling. Production of components of the ECM constitutes one of the central demands and challenges to the secretory pathway, highlighting the production of collagens. It is quite remarkable to notice that in this report the intersection of genes regulated by XBP1s and TMEM2 involve many components of the ECM. Developmental studies demonstrated that most of the abnormal phenotypes triggered by the genetic disruption of UPR mediators is due to the accumulation of misfolded collagens (Rojas-Rivera et al., 2018). ER stress regulates the production of ECM, and components of the collagen-production machinery were recently coupled to the ER stress-sensing mechanism (Boot-Handford and Briggs, 2010). Whether ER stress or the UPR affects the production of HA is unknown. We speculate that an intricate connection emerged during evolution to tightly regulate ECM stability and maintenance of ER proteostasis through TMEM2 and the UPR.

The implications of this study are exciting because they offer a previously unanticipated link among ER stress, the extracellular matrix, and their effects on organismal health and survival. However, it remains to be demonstrated whether either the TMEM2 pathway or the UPR is a relevant factor controlling mammalian aging. The current study suggests that interventions in the proposed TMEM2-regulated pathway, for example by the administration of low-molecular-weight HA molecules, could be used as a strategy to protect cells against chronic ER stress in aging and disease.

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REFERENCES

Balch, W.E., Morimoto, R.I., Dillin, A., and Kelly, J.W. (2008). Adapting proteostasis for disease intervention. Science *319*, 916–919.

Boot-Handford, R.P., and Briggs, M.D. (2010). The unfolded protein response and its relevance to connective tissue diseases. Cell Tissue Res. *339*, 197–211.

Cyphert, J.M., Trempus, C.S., and Garantziotis, S. (2015). Size Matters: Molecular Weight Specificity of Hyaluronan Effects in Cell Biology. Int. J. Cell Biol. *2015*, 563818.

Henis-Korenblit, S., Zhang, P., Hansen, M., McCormick, M., Lee, S.J., Cary, M., and Kenyon, C. (2010). Insulin/IGF-1 signaling mutants reprogram ER stress response regulators to promote longevity. Proc. Natl. Acad. Sci. USA *107*, 9730–9735.

Hetz, C. (2012). The unfolded protein response: controlling cell fate decisions under ER stress and beyond. Nat. Rev. Mol. Cell Biol. *13*, 89–102.

Kennedy, B.K., Berger, S.L., Brunet, A., Campisi, J., Cuervo, A.M., Epel, E.S., Franceschi, C., Lithgow, G.J., Morimoto, R.I., Pessin, J.E., et al. (2014). Geroscience: linking aging to chronic disease. Cell *159*, 709–713.

Martínez, G., Duran-Aniotz, C., Cabral-Miranda, F., Vivar, J.P., and Hetz, C. (2017). Endoplasmic reticulum proteostasis impairment in aging. Aging Cell *16*, 615–623.

Rojas-Rivera, D., Rodriguez, D.A., Sepulveda, D., and Hetz, C. (2018). ER stress sensing mechanism: Putting off the brake on UPR transducers. Oncotarget *9*, 19461–19462.

Schinzel, R.T., Higuchi-Sanabria, R., Shalem, O., Moehle, E.A., Webster, B.M., Joe, L., Bar-Ziv, R., Frankino, P.A., Durieux, J., Pender, C., et al. (2019). The Hyaluronidase, TMEM2, Promotes ER Homeostasis and Longevity Independent of the UPRER. Cell *179*, this issue, 1306–1318.

Taylor, R.C., and Dillin, A. (2013). XBP-1 is a cell-nonautonomous regulator of stress resistance and longevity. Cell *153*, 1435–1447.

Wang, M., and Kaufman, R.J. (2016). Protein misfolding in the endoplasmic reticulum as a conduit to human disease. Nature *529*, 326–335.

Yamaguchi, Y., Yamamoto, H., Tobisawa, Y., and Irie, F. (2019). TMEM2: A missing link in hyaluronan catabolism identified? Matrix Biol. *78-79*, 139–146.

RNA-Binding Proteins Chaperone Ribonucleoprotein Complex Assembly to Solve the RNA-Folding Problem

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The inherent tendency of RNAs to misfold is a major problem that can impede efficient assembly of essential ribonucleoprotein complexes (RNPs), such as ribosomes. In this issue of *Cell*, Duss et al., (2019) and Rodgers and Woodson (2019) reveal how transient RNA-protein interactions can chaperone RNA folding during RNP assembly.

RNAs and ribonucleoprotein complexes (RNPs) are essential for gene expression, a process that defines cell types and enables cellular adaptation. A hallmark of RNA molecules is their outstanding flexibility, both functionally and structurally. Beyond classical Watson-Crick base-pairing interactions that enable formation of local secondary structure elements (e.g., hairpins), all RNA nucleotides can engage in hydrogen bonding and other electrostatic interactions that allow formation of intricate tertiary structures, including helices and multi-way junctions. Importantly, such interactions not only take place between proximal RNA sequences but can also bridge long distances in RNA sequences. These specialized physical properties of RNAs can endow them with catalytic activity and render them ideal scaffolds for large RNPs, such as ribosomes and spliceosomes. However, a major caveat of such conformational flexibility is an inherent tendency to form relatively stable, non-desirable interactions that can act as kinetic traps and impede efficient assembly of mature RNA/RNP structures. It has been suggested that this propensity, often termed the "RNA-folding problem" (Herschlag, 1995), can be overcome by strategies such as the co-transcriptional assembly of RNPs, which allows the 5′ ends of RNAs to fold correctly and early RNA-binding proteins (RBPs) to associate prior to the synthesis of downstream RNA sequences that could otherwise form non-native interactions (Pan and Sosnick, 2006). Furthermore, RNA chaperones, such as Hfq, and energy-dependent enzymes such as RNA helicases have been shown to help overcome RNA misfolding by destabilizing aberrant secondary structures and/or regenerating single-stranded regions allowing a misfolded RNA a new chance at correct assembly (Jarmoskaite and Russell, 2014; Woodson et al., 2018). Nevertheless, several studies comparing the kinetics of *in vitro*-reconstituted RNP assembly systems with the dynamics of RNP assembly