Better to burn out than it is to rust: coordinating cellular redox states during aging and stress

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Both the protein homeostasis (proteostasis) and the oxidation/reduction (redox) environment of the cell play critical roles in disease- and age-associated decline, yet the relationship between the two remains mysterious. In this issue of *The EMBO Journal*, Kirstein et al (2015) show that both the cytosol and the ER shift their redox states in response to proteotoxic stress and that stress in one compartment can alter redox state in the other. Moreover, proteotoxic stress can induce changes in redox state across tissues, suggesting that an organism-wide surveillance mechanism modulates cellular redox environment.

See also: J Kirstein et al

Cellular physiology runs on the machinery of proteins, yet proteins are susceptible to a variety of damage, including unfolding, aggregation, oxidation, and glycation. Thus, cells must use mechanisms to maintain a functional proteome and overall protein homeostasis (proteostasis). One of the hallmarks of aging is the gradual loss of proteostasis over time, and multiple neurological disorders exhibit symptoms of impaired proteostasis. Whether the loss of proteostasis is a cause or a consequence (or both) of physiological decline in these disorders or during natural aging remains a topic of debate.

Proteostasis is maintained through a three-pronged strategy of prevention, repair, and damage control. For cytosolic proteins, protein damage is prevented by oxidoreductases, which maintain the cytosol in a reducing environment, preventing the oxidation of proteins and other macromolecules. The cytosolic proteome is also regularly repaired by heat-shock response (HSR) proteins, which facilitate protein folding and disassemble protein aggregates. Damaged and unfolded cytosolic proteins are removed by the ubiquitin–proteasome system (UPS), which tags and degrades such proteins, and autophagy, which removes aggregation-prone proteins that escape degradation.

Integral membrane proteins are exposed to the extracellular milieu, which is a more oxidizing environment relative to the cytosol. Membrane proteins are often rich in oxidized disulfide bonds; thus, the lumen of the ER must be maintained as a relatively oxidizing environment through the action of protein disulfide isomerases (PDIs) and oxidoreductases like ERO1 and peroxiredoxin-4 (Araki & Nagata, 2011). Membrane proteins that fail to have their disulfide bonds oxidized (or fail to fold for other reasons) trigger the induction of the unfolded protein response (UPR), which activates the expression of ER-resident heat-shock proteins to mediate refolding, and ER-associated degradation (ERAD), which removes misfolded proteins (Dufey et al, 2014).

Multiple proteostasis mechanisms are induced in response to specific proteotoxic stressors. In the case of the HSR and UPR, it appears that proteotoxic stress in one tissue can modulate the activity of these proteostasis mechanisms in other tissues, although the exact transcellular signal remains unclear (van Oosten-Hawle & Morimoto, 2014). We do not know whether similar transcellular signaling modulates redox states across tissues. Indeed, we do not know whether the redox states between the ER and the cytosol are coordinated, or how that coordination changes over time or in disease states. A particularly important question is whether and how redox states are adjusted in response to proteotoxic stress.

In their article in this issue of *The EMBO Journal*, Kirstein et al (2015) use the model organism *C. elegans* to examine coordination of redox states between subcellular compartments as well as between tissues. The authors take advantage of *C. elegans* transparency by generating transgenes that express GFP-based sensors for redox state and peroxide levels. They examine not only different tissues (e.g. neurons versus muscle using tissue-specific promoters for expression) but also different subcellular compartments (e.g. cytosol versus ER). And the authors go to great lengths to validate these reagents, exposing transgenic nematodes to reducing or oxidizing agents to obtain the expected changes in fluorescence excitation and emission in their reporters. They also conduct parallel studies in HeLa cells, allowing them to test whether their findings extend to human cells.

With these reagents in hand, the authors ask what happens to the redox environment when animals undergo proteotoxic stress (Fig 1). They generate such stress in the cytosol by expressing several different metastable proteins. They also generate proteotoxic stress in the ER by using RNAi to
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Figure 1. Summary of key experiments exploring the relationship between proteotoxic stress and cellular redox environment.

Unstressed cells (left) have ER compartments that are relatively more oxidizing (indicated by the rust color) than the reducing environment (indicated by the silver color) in the cytosol. Proteotoxic stress (e.g. protein aggregates and unfolded proteins, indicated in yellow) in the ER (middle, top), cytosol (middle, middle), or in other tissues (middle, bottom) results in shifts in redox environment in both the ER, which becomes more reducing, and the cytosol, which becomes more oxidizing (right).

As animals age, they accumulate protein aggregates as proteostasis mechanisms slowly recede (Lapierre & Hansen, 2012; Labbadia & Morimoto, 2015). The authors therefore examine redox states in aging C. elegans, focusing on muscle. Surprisingly, the redox state in both the ER and the cytosol fluctuates multiple times during development. However, once development is complete and the period of peak fecundity has passed, the ER and cytosol slowly become more reduced and oxidized, respectively, mimicking the states observed in younger animals exposed to proteotoxic stress. Known mutants that either extend or reduce life span in turn delay or accelerate the timing of this shift in redox state, respectively, further supporting previous findings that correlated aging and redox state (Back et al., 2012; Knoefler et al., 2012).

Finally, the authors examine whether stress in one tissue can affect the redox state in another, mirroring multiple studies that previously demonstrated non-autonomous regulation of stress response pathways (van Oosten-Hawle & Morimoto, 2014). Expression of polyglutamine repeats in muscle induces a shift to more oxidizing cytosolic conditions in neurons. Likewise, polyglutamine expression in neurons evokes a similar redox shift in muscle. Thus, proteotoxic stress in the cytosol of one tissue can trigger changes in the redox state of another tissue, implying the existence of an organism-wide signaling mechanism for regulating redox state.

Some interesting questions remain. Does the proteotoxicity that occurs during aging trigger the changes in redox state, or is this just a correlation? Does the transcellular signaling that regulates cytosolic redox state also extend to the ER redox state? And what is the signal between tissues and, for that matter, between subcellular compartments? Damage to compartment membranes that results in the leakage of oxidizing and reducing agents, as well as damage to the machinery that maintains compartmental redox states, could provide a passive transcompartmental signal. The transcellular signal could also be passive (e.g. the release of protein aggregates contained in exosomes) or active (e.g. the release of an endocrine-like molecule). Finally, what are the consequences of such redox modulation, and why would cells want to make their ER more reducing and their cytosol more oxidizing—conditions that one might expect would make proteotoxicity worse—when they (or neighboring cells) experience proteotoxic stress? Regardless of the answers to these questions, this study further highlights that proteostasis can be regulated in an organism-wide fashion, which has important implications for understanding aging and disease.

References


