

Proteostasis Takes Center Stage in Pulmonary Fibrosis

The proteostasis network consists of a large number of specialized proteins that are necessary for the precise function of processes that oversee the life cycle of all cellular proteins (1). Newly translated proteins are folded into their native state through the action of molecular chaperones, and trafficked to specific subcellular locations. Proteins that are damaged or not needed are degraded via the ubiquitin proteasome or lysosomal degradation systems (2). Disruption of the proteostasis network at any point presents a major challenge to the intracellular proteome, simultaneously causing a relative imbalance in functional levels of critical proteins in subcellular compartments and the accumulation of misfolded or damaged proteins that are prone to aggregate or precipitate in the remarkably protein-rich intracellular environment (3).

In humans, the molecular "chaperome" is comprised of some 332 genes that serve promiscuous roles in protein folding (4). These chaperones include canonical members of the heat shock protein (HSP) family as well as proteins involved in organelle-specific folding in the endoplasmic reticulum and the mitochondria. Chaperones are expressed continuously in most cells but are robustly induced upon environmental (e.g., heat shock) or organelle-specific stress (e.g., endoplasmic reticulum stress or the mitochondrial unfolded protein response). Genetic studies hint at proteostatic stress in the lung epithelium as a potential driver of many lung diseases, including pulmonary fibrosis (5, 6). For example, mutations in the gene encoding SFTPC that cause misfolding of the protein have been observed in families with increased rates of idiopathic pulmonary fibrosis (7). An autosomal-recessive mutation that results in a defect in vesicular trafficking results in Hermansky-Pudlak syndrome, which is associated with highly penetrant pulmonary fibrosis (8). Although direct evidence of a protein folding defect has not been shown, a common variant SNP in the promoter region of the gene encoding an abundantly expressed mucin, MUC5B, is associated with increased expression of the protein and an increased risk of pulmonary fibrosis (9). The chronic proteostatic stress associated with these mutations might be expected to induce the expression of chaperones in the lung as part of an adaptive response. Consistent with this hypothesis, genetic loss of HSP70 (*Hspa1a*) in mice has been reported to increase susceptibility to bleomycin-induced fibrosis (10).

In this issue of the *Journal*, Sellares and colleagues (pp. 629–636) report on the expression of HSP70 in lung tissues and primary human lung fibroblasts obtained from patients with pulmonary fibrosis (11). Contrary to predictions, the expression of constitutive and inducible HSP70 was reduced in lung tissue from patients with pulmonary fibrosis compared with normal control subjects and in primary cultured fibroblasts from the lungs of patients with pulmonary fibrosis. The investigators go on to show that administration of the profibrotic cytokine TGF- β or viral transfection of IGFBP5 reduced the expression of both constitutive

and inducible HSP70. They suggest that the loss of HSP70 in the fibrotic environment removed an inhibitory effect on TGF- β signaling that promoted the production of matrix proteins by lung fibroblasts. Consistent with a protective role of HSP70 in fibrosis, global deletion of the inducible form of HSP70 worsened bleomycin-induced fibrosis in mice.

The work by Sellares and colleagues extends the larger body of work implicating dysfunction in the proteostasis network in the development of fibrosis, and at the same time raises questions. Perhaps most importantly, the investigators suggest that signaling induced by profibrotic cytokines in the microenvironment might inhibit the expression of chaperones to worsen proteostatic stress, potentially creating a self-sustaining cycle of fibrosis. Substantial additional work, however, will need to be done before such a conclusion can be made. For example, although chaperones are expressed in virtually every cell, their regulation during stress is likely cell-type specific (12). Careful studies in which chaperones are deleted within specific cell types will be required to address these questions. Furthermore, although the expression of HSP70 was reduced in the end-stage fibrotic tissues examined by Sellares and colleagues, it is not clear whether this represents an early event in the pathogenesis of fibrosis or later stages of the disease. For example, expression of a mutant of the gene encoding CFTR that causes cystic fibrosis in airway epithelial cells acutely induces an adaptive chaperone response, but chronic expression results in global dysfunction in protein folding (13). In addition, the observation that impaired HSP70 expression persists in lung fibroblasts from patients with pulmonary fibrosis after removal from the fibrotic microenvironment hints at epigenetic changes that impair chaperone responses; however, the mechanisms that underlie this observation are not known.

The work by Sellares also raises questions about the enhanced susceptibility to pulmonary fibrosis with aging. A substantial body of literature suggests that dysfunction in the proteostasis network is a major driver of age-related phenotypes that might be programmed by conserved signaling events (14, 15). In a study of human brains, Brehme and colleagues found reduced mRNA expression of chaperones in normal aging and in patients with dementia (4). Indeed, Sellares and colleagues suggest that adult mice lacking inducible HSP70 are slightly more susceptible to fibrosis than juvenile mice. Systematic studies to examine both the expression and function of proteostasis genes during aging will be required to address these questions. ■

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References

- Balch WE, Morimoto RI, Dillin A, Kelly JW. Adapting proteostasis for disease intervention. *Science* 2008;319:916–919.
- Sala AJ, Bott LC, Morimoto RI. Shaping proteostasis at the cellular, tissue, and organismal level. *J Cell Biol* 2017;216:1231–1241.
- Morimoto RI, Cuervo AM. Proteostasis and the aging proteome in health and disease. *J Gerontol A Biol Sci Med Sci* 2014;69:S33–S38.
- Brehme M, Voisine C, Rolland T, Wachi S, Soper JH, Zhu Y, *et al.* A chaperone subnetwork safeguards proteostasis in aging and neurodegenerative disease. *Cell Rep* 2014;9:1135–1150.
- Balch WE, Sznajder JL, Budinger S, Finley D, Laposky AD, Cuervo AM, *et al.* Malfolded protein structure and proteostasis in lung diseases. *Am J Respir Crit Care Med* 2014;189:96–103.
- Kropski JA, Blackwell TS, Loyd JE. The genetic basis of idiopathic pulmonary fibrosis. *Eur Respir J* 2015;45:1717–1727.
- Lawson WE, Grant SW, Ambrosini V, Womble KE, Dawson EP, Lane KB, *et al.* Genetic mutations in surfactant protein C are a rare cause of sporadic cases of IPF. *Thorax* 2004;59:977–980.
- El-Chemaly S, Young LR. Hermansky-Pudlak syndrome. *Clin Chest Med* 2016;37:505–511.
- Hunninghake GM, Hatabu H, Okajima Y, Gao W, Dupuis J, Latourelle JC, *et al.* MUC5B promoter polymorphism and interstitial lung abnormalities. *N Engl J Med* 2013;368:2192–2200.
- Tanaka K, Tanaka Y, Namba T, Azuma A, Mizushima T. Heat shock protein 70 protects against bleomycin-induced pulmonary fibrosis in mice. *Biochem Pharmacol* 2010;80:920–931.
- Sellares J, Veraldi KL, Thiel KJ, Cárdenes N, Alvarez D, Schneider F, *et al.* Intracellular heat shock protein 70 deficiency in pulmonary fibrosis. *Am J Respir Cell Mol Biol* 2019;60:629–636.
- Hartl FU, Bracher A, Hayer-Hartl M. Molecular chaperones in protein folding and proteostasis. *Nature* 2011;475:324–332.
- Roth DM, Hutt DM, Tong J, Boucheccareilh M, Wang N, Seeley T, *et al.* Modulation of the maladaptive stress response to manage diseases of protein folding. *PLoS Biol* 2014;12:e1001998.
- Taylor RC, Dillin A. Aging as an event of proteostasis collapse. *Cold Spring Harb Perspect Biol* 2011;3:a004440.
- Labbadia J, Morimoto RI. Repression of the heat shock response is a programmed event at the onset of reproduction. *Mol Cell* 2015;59:639–650.