Choosing the right response to ER stress

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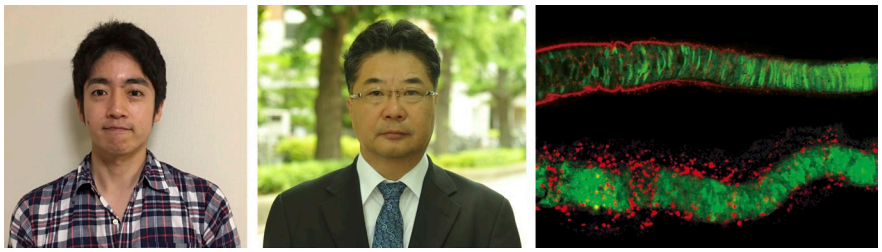
Cells use distinct unfolded protein response transducers to export different collagens during development.

The accumulation of unfolded or misfolded secretory proteins in the endoplasmic reticulum triggers the unfolded protein response (UPR), in which a number of different transducer proteins can be activated to induce the expression of ER-localized chaperones to assist in protein folding or up-regulate genes that promote protein degradation. Ishikawa et al. reveal that cells can activate different UPR transducers at different developmental stages, depending on the secretory cargo they are having trouble folding (1).



Focal Point Tokiro Ishikawa (left), Kazutoshi Mori (right), and colleagues reveal that, during medaka fish development, notochord cells activate different transducers of the unfolded protein response, depending on the developmental stage and the secretory cargo that is causing ER stress. Early notochord cells activate ATF6 to promote the folding and secretion of short-chain type VIII collagen. Subsequently, notochord sheath cells activate not only ATF6 but also BBF2H7 to fold and package long-chain type II collagen into specially enlarged COPII vesicles. Wild-type fish (right, top) form a vacuolated notochord (green) surrounded by a basement membrane containing type II collagen (red). In fish lacking BBF2H7 (right, bottom), type II collagen is retained in notochord sheath cells, which disrupts basement membrane assembly and causes notochord bending. Photos and microscopy image courtesy of the authors.

Though the UPR can be triggered by stresses that cause protein misfolding, such as inhibition of protein glycosylation, the pathway can also be activated during normal development, when specific cell types begin to secrete large amounts of particular cargoes (2). For example, Tokiro Ishikawa, Kazutoshi Mori, and colleagues at Kyoto University have shown that the UPR is required early in medaka fish development, when disk-like notochord cells secrete large amounts of short-chain type VIII collagen to correctly align and form the notochord (3). Fish lacking both the α and β isoforms of the UPR transducer ATF6 fail to up-regulate the ER chaperones necessary to mediate type VIII collagen folding, and therefore fail to form the notochord, which serves as the body's axis before the vertebrae are formed.

ATF6 α and β are ubiquitously expressed ER membrane proteins that, upon ER stress, are proteolytically cleaved to liberate N-terminal fragments that translocate into the nucleus to activate chaperone gene transcription. However, similar to mammals, medaka fish show tissue-specific expression of five other ATF6-like proteins. "Why are so many UPR transducers required if ER stress simply means the accumulation of misfolded proteins in the ER?" Mori asks.

To begin addressing this question, Ishikawa et al. identified medaka fish lacking an ATF6-like protein called BBF2H7 (1). These fish managed to align their disk-like notochord cells correctly, but they appeared to fail a subsequent step in notochord development, when the disk-like cells differentiate into either large, vacuolated cells or epithelial sheath cells. The latter cell type secretes long-chain type II collagen to form a basement membrane that, together with the vacuolated cells, makes the notochord rigid. Ishikawa et al. found that BBF2H7 was normally expressed in sheath cells, and that medaka fish lacking this ATF6-like UPR transducer were unable to assemble a basement membrane, resulting in the formation of short, bent notochords.

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Instead of being secreted, type II collagen appeared to be trapped in the ER of sheath cells lacking BBF2H7. Unlike type VIII collagen, which can be folded into a compact structure that can be exported from the ER in regular-sized COPII vesicles, type II collagen is a longer, more rigid molecule that can only be exported in specially enlarged COPII carriers. (see the paper by Gorur et al., also in this issue, visualizing similar carriers transporting procollagen I molecules [4]). Ishikawa et al. found that BBF2H7 up-regulates all of the genes required for the formation of enlarged COPII vesicles, including COPII coat components and the collagen receptor Tango1.

Notochord sheath cells therefore activate BBF2H7 to facilitate the export of long-chain type II collagen in large COP II vesicles. Ishikawa et al. found that these cells also require ATF6 to up-regulate the ER chaperones that mediate type II collagen folding. In contrast, earlier in development, disk-like notochord cells only require ATF6 to promote the folding of short-chain type VIII collagen, which can be exported in normal-sized COPII vesicles.

"The next critical issue is to understand how the ER discriminates the difference in length of synthesized collagen to activate BBF2H7," Mori says. "In particular, it will be intriguing to determine whether BBF2H7 itself recognizes the difference, or whether some other molecules sense the difference and relay the signal to BBF2H7." Mori and colleagues also plan to examine the function of every other UPR transducer in medaka fish development.

1. Ishikawa, T., et al. 2017. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201609100
2. Walter, P., and D. Ron. 2011. *Science.* 334:1081–1086.
3. Ishikawa, T., et al. 2013. *Mol. Biol. Cell.* 24:1387–1395.
4. Gorur, A., et al. 2017. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201702135

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