translated proteins require oxygen to form disulfide bonds, Koritzinsky et al. reveal, which may explain why low oxygen levels activate the unfolded protein response (UPR).

The UPR alleviates stress in the endoplasmic reticulum (ER) by suppressing translation and up-regulating chaperones and other factors that promote protein folding in the ER lumen. The fact that hypoxia induces the UPR suggests that oxygen is somehow required for the ER to process and export secretory cargo. But which of the ER’s many activities depends on oxygen is unknown.

Koritzinsky et al. followed the maturation and transport of several secretory proteins in hypoxic cells and found that the absence of oxygen didn’t inhibit protein glycosylation or vesicle transport. But low oxygen levels did impair the ability of newly synthesized proteins to form disulfide bonds, a critical step in the folding and maturation of many secretory proteins.

Disulfide bonds are introduced by a redox relay involving ER-localized protein disulfide isomerases (PDIs) and oxidases. The process can start while an ER cargo protein is still being translated but continues post-translationally, with multiple cysteine residues breaking and re-forming disulfide bonds until the correct conformation is achieved. Oxygen has been shown to accept the electrons that pass through PDIs and oxidases when disulfide bonds are formed in vitro. Koritzinsky et al. found that, in vivo, oxygen was only required for the formation of post-translational disulfide bonds, suggesting that disulfide bonds formed during translation are created by distinct PDIs and oxidases that can use an alternative electron acceptor. The researchers now want to identify these enzymes and to determine what electron acceptor they use instead of oxygen.

Koritzinsky, M., et al. 2013. J. Cell Biol. http://dx.doi.org/10.1083/jcb.201307185.

Disulfide bonds are introduced by a redox relay involving ER-localized protein disulfide isomerases (PDIs) and oxidases. The process can start while an ER cargo protein is still being translated but continues post-translationally, with multiple cysteine residues breaking and re-forming disulfide bonds until the correct conformation is achieved. Oxygen has been shown to accept the electrons that pass through PDIs and oxidases when disulfide bonds are formed in vitro. Koritzinsky et al. found that, in vivo, oxygen was only required for the formation of post-translational disulfide bonds, suggesting that disulfide bonds formed during translation are created by distinct PDIs and oxidases that can use an alternative electron acceptor. The researchers now want to identify these enzymes and to determine what electron acceptor they use instead of oxygen.

Koritzinsky, M., et al. 2013. J. Cell Biol. http://dx.doi.org/10.1083/jcb.201307185.