Journal club

ENTERING A NEW ERA WITH ERO

Sometimes a discovery changes everything. Like the car changed the world. Like photography changed our collective memory. In a similar way, the discovery of the sulfhydryl oxidase Ero1 (endoplasmic oxidoreductin 1) by the laboratories of Chris Kaiser and Jonathan Weissman, through a yeast genetic screen a decade ago, changed the endoplasmic reticulum (ER) world forever. A new era began.

> “…the discovery of the sulfhydryl oxidase Ero1… changed the endoplasmic reticulum (ER)-world forever.”

Before Ero1 we knew that the ER is oxidizing and the cytosol is reducing, and that proteins in the cytosol have free cysteines and secretory proteins have disulphide bonds. We also knew that glutathione buffers the cytosol against hyperoxidation and that oxidized glutathione supports disulphide bond formation during protein refolding *in vitro*. We thought that the oxidizing ER milieu arose from the import of oxidized glutathione, and that oxidized glutathione was sufficient for disulphide bond formation during protein folding in the ER.

This knowledge was turned upside down in the Ero1 era. We now know that protein disulphide bond formation is actually catalysed by redox enzymes, which are kept active by Ero1. We also know that glutathione buffers both the cytosol and the ER against hyperoxidation and that, although glutathione can support oxidative folding *in vitro*, it does not do so *in vivo*. Two papers therefore changed our thinking by 180°.

But knowledge in science is the truth of the day. So where are we now and where will we be? Small redox molecules, such as oxidized glutathione, and redox enzymes that are kept active by Ero1 may both be working *in vivo*. In addition, Ero1 may be less omnipotent than first thought, as the sulfhydryl oxidases Erv2 and QSOX (in mammals) oxidize proteins in parallel with Ero1. Regardless, we enjoyed the years in which an elegant ER-world-changing discovery overhauled our thinking and made us believe.

Ineke Braakman
Cellular Protein Chemistry, Faculty of Science, Utrecht University, Padualaan 8, NL-3584 CH Utrecht, The Netherlands.
e-mail: i.braakman@uu.nl

ORIGINAL RESEARCH PAPERS Frand, A. R. & Kaiser, C. A. The *ERO1* gene of yeast is required for oxidation of protein dithiols in the endoplasmic reticulum. *Mol. Cell* **1**, 161–170 (1998) | Pollard, M. G. *et al.* Ero1p: a novel and ubiquitous protein with an essential role in oxidative protein folding in the endoplasmic reticulum. *Mol. Cell* **1**, 171–182 (1998)