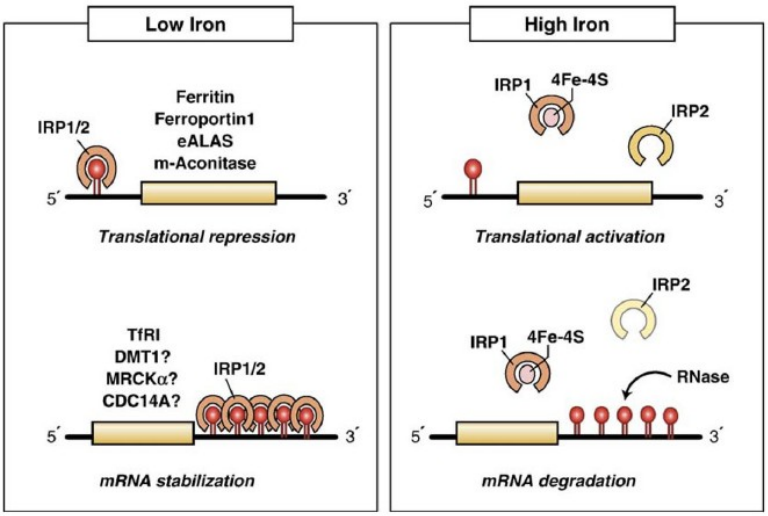
THE LANCET Neurology

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Ward RJ , Zucca FA, Duyn JH, Crichton RR, Zecca L. The role of iron in brain ageing and neurodegenerative disorders. *Lancet Neurol* 2014; **13:** 1045–60.

Supplementary Figure 1: IRP/IRE regulation of cellular iron homeostasis. IRPs bind to iron regulatory elements (IREs) located in either the 5′– or 3′–untranslated regions (UTRs) of specific mRNAs. When iron is in short supply, the IRPs bind to IREs, in mRNAs of the regulated proteins. If the IREs are in the 5'–UTR of the mRNA, (e.g., Ft and Fpn), binding of IRPs prevents initiation of translation. In contrast, when the IREs are in the 3'–UTR, as in the case of TfR1 and DMT1, binding of the IRPs protects the mRNAs against nuclease degradation.[1] This results in increased iron uptake and impaired iron storage and export. When iron is abundant, the IRPs are no longer active in binding, allowing Ft and Fpn mRNAs to be translated and resulting in the nuclease–catalysed degradation of TfR1 and DMT1 mRNAs. Under these conditions, IRP1 acquires aconitase activity, associated with the incorporation of a iron–sulfur cluster (4Fe–4S), whereas IRP2 is degraded after ubiquitination in the proteasome.[2–4] Reproduced from Wallander,[1] by permission of Elsevier Limited.



Reference list

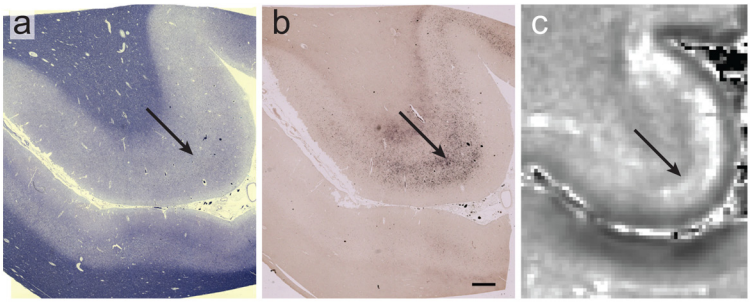
1 Wallander ML, Leibold EA, Eisenstein RS. Molecular control of vertebrate iron homeostasis by iron regulatory proteins. *Biochim Biophys Acta* 2006; **1763**: 668–689.

2 Crichton, R.R. Inorganic Biochemistry of Iron Metabolism From Molecular Mechanisms to Clinical Consequences. John Wiley & Sons, Ltd pp. 461 Chichester, UK (2009).

3 Muckenthaler MU, Galy B, Hentze MW. Systemic iron homeostasis and the iron-responsive element/iron-regulatory protein (IRE/IRP) regulatory network. Annu Rev Nutr 2008; 28: 197–213.

4 Zucca FA, Cupaioli FA, Zecca L. The Role of Iron in Neurodegeneration. pp. 174-211. In: “Neurodegeneration: Metallostasis and Proteostasis”. In the series: “RSC Drug Discovery”. Editors: Danilo Milardi, Enrico Rizzarelli. RSC Publishing, UK, July 21, 2011.

Supplementary Figure 2: **abnormal iron distribution in motor cortex tissue from amyotrophic lateral sclerosis patient.** Luxol fast blue myelin (A) and Perls' DAB iron stain (B) compared with R_2* (= $1/T_2$*) relaxation rate from post–mortem 7T MRI (C). A unique pattern of intra–cortical and subcortical bands of iron is observed that correlate with R_2*. Scale bar 1 mm (in B). Modified from Kwan,[1] by permission of PLoS ONE.



Reference list

1 Kwan JY, Jeong SY, Van Gelderen P, et al. Iron accumulation in deep cortical layers accounts for MRI signal abnormalities in ALS: correlating 7 tesla MRI and pathology. *PLoS One* 2012; **7**: e35241.