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Genetic ablations of iron regulatory proteins 1 and 2 reveal why iron regulatory protein 2 dominates iron homeostasis

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The two iron regulatory proteins IRP1 and IRP2 bind to transcripts of ferritin, transferrin receptor and other target genes to control the expression of iron metabolism proteins at the post-transcriptional level. Here we compare the effects of genetic ablation of IRP1 to IRP2 in mice. IRP1−/− mice misregulate iron metabolism only in the kidney and brown fat, two tissues in which the endogenous expression level of IRP1 greatly exceeds that of IRP2, whereas IRP2−/− mice misregulate the expression of target proteins in all tissues. Surprisingly, the RNA-binding activity of IRP1 does not increase in animals on a low-iron diet that is sufficient to activate IRP2. In animal tissues, most of the bifunctional IRP1 is in the form of cytosolic aconitase rather than an RNA-binding protein. Our findings indicate that the small RNA-binding fraction of IRP1, which is insensitive to cellular iron status, controls mitochondrial aconitase and other members of the aconitase family (Gruen et al., 1997), the enzymatic form of IRF1 contains a (4Fe-4S)2+ cluster prosthetic group at its catalytic center, and interconverts citrate and iso-citrate (Kennedy et al., 1992). Although IRP1 is only 22% identical to mitochondrial aconitase in peptide sequence (Rouault et al., 1991), its enzymatic specific activities with all three substrates are very similar to those of mitochondrial aconitase (Kennedy et al., 1992). However, unlike mitochondrial aconitase, the role of cytosolic aconitase in mammalian cellular metabolism remains poorly understood. IRP1 homologs are found in numerous organisms, including Caenorhabditis elegans (Gourley et al., 2003) and Drosophila melanogaster (Muckenthaler et al., 1998), but there are no IRP1 homologs in yeast.

In mammals, IRP1 is one of two iron regulatory proteins (IRP1 and IRP2) that bind to RNA stem-loop elements known as iron-responsive elements (IREs) found within transcripts that encode several iron metabolism proteins. IRP binding to IREs within 3′UTRs of transcripts such as ferritin results in translational repression, whereas binding to IREs in the 3′UTR of the transferrin receptor (TIR) results in stabilization of the transcript. Thus, IRPs coordinate the cellular response to iron depletion by decreasing iron storage and increasing iron uptake (Henzie and Kahn, 1996; Rouault and Klauser, 1997; Schneider and Leibold, 2000). IRP1 and IRP2 share high sequence homology and exhibit very similar biochemi...