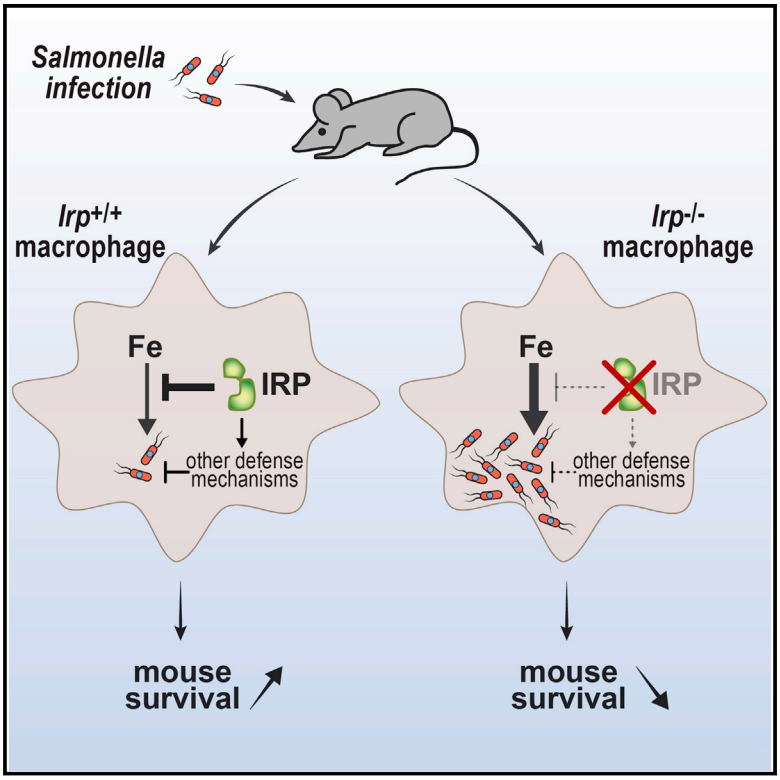
Short Article

Cell Host & Microbe

Iron Regulatory Proteins Mediate Host Resistance to *Salmonella* Infection

Graphical Abstract



Authors

Manfred Nairz, Dunja Ferring-Appel, Daniela Casarrubea, ..., Matthias W. Hentze, Guenter Weiss, Bruno Galy

Correspondence

hentze@embl.de (M.W.H.), guenter.weiss@i-med.ac.at (G.W.)

In Brief

Pathogens require iron to proliferate in vivo. Nairz and Ferring-Appel et al. show that macrophage-specific ablation of iron regulatory proteins 1 and 2, RNA-binding factors that orchestrate mammalian iron metabolism, impairs innate immunity against *Salmonella* in mice, in part due to failure of the host to limit microbial iron acquisition.

Highlights

- IRPs control key molecules of iron sequestration and transport in macrophages
- Macrophage IRP function is dispensable for maintaining steady-state body iron balance
- Macrophage IRPs protect mice against infection with *Salmonella* Typhimurium
- IRPs restrict intracellular *Salmonella* growth by at least two mechanisms

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Iron Regulatory Proteins Mediate Host Resistance to *Salmonella* Infection

Manfred Nairz,[1,5,6] Dunja Ferring-Appel,[2,5] Daniela Casarrubea,[2] Thomas Sonnweber,[1] Lydie Viatte,[2] Andrea Schroll,[1] David Haschka,[1] Ferric C. Fang,[3,4] Matthias W. Hentze,[2,*] Guenter Weiss,[1,*] and Bruno Galy[2,7]

[1]Department of Internal Medicine VI, Infectious Diseases, Immunology, Rheumatology, and Pneumology, Medical University of Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria
[2]European Molecular Biology Laboratory, Meyerhofstrasse 1, 69117 Heidelberg, Germany
[3]Department of Laboratory Medicine
[4]Department of Microbiology
University of Washington, Seattle, WA 98195-7735, USA
[5]Co-first author
[6]Present address: Center for Systems Biology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA
[7]Present address: Deutsches Krebsforschungszentrum Heidelberg, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany
*Correspondence: hentze@embl.de (M.W.H.), guenter.weiss@i-med.ac.at (G.W.)
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SUMMARY

Macrophages are essential for systemic iron recycling, and also control iron availability to pathogens. Iron metabolism in mammalian cells is orchestrated posttranscriptionally by iron-regulatory proteins (IRP)-1 and -2. Here, we generated mice with selective and combined ablation of both IRPs in macrophages to investigate the role of IRPs in controlling iron availability. These animals are hyperferritinemic but otherwise display normal clinical iron parameters. However, mutant mice rapidly succumb to systemic infection with *Salmonella* Typhimurium, a pathogenic bacterium that multiplies within macrophages, with increased bacterial burdens in liver and spleen. Ex vivo infection experiments indicate that IRP function restricts bacterial access to iron via the EntC and Feo bacterial iron-acquisition systems. Further, IRPs contain *Salmonella* by promoting the induction of lipocalin 2, a host antimicrobial factor that inhibits bacterial uptake of iron-laden siderophores, and by suppressing the ferritin iron pool. This work reveals the importance of the IRPs in innate immunity.

INTRODUCTION

Iron supply for the hemoglobinization of new red blood cells in the erythroid marrow depends largely on recycling of the metal by the liver and spleen monocyte-macrophage system (MPS), which clears old erythrocytes, frees iron from hemoglobin, and exports the metal back into the circulation through the iron exporter ferroportin (FPN, a.k.a. SLC40A1) (Ganz, 2013). Iron recycling by the MPS diminishes in response to infection, which is viewed as an innate defense mechanism to reduce the iron concentration in the circulation and thereby withhold the metal from invaders (Drakesmith and Prentice, 2012; Nairz et al., 2014). Macrophage iron metabolism is thus critical both for securing body iron sufficiency and immunity.

Systemic iron fluxes are controlled in part by the hormone hepcidin (a.k.a. HAMP), which inhibits iron export from macrophages by binding to and triggering the degradation of FPN (Nemeth et al., 2004). In addition to humoral control of systemic iron metabolism by hepcidin, iron metabolism is also regulated cellularly by the iron regulatory proteins (IRP)-1 and -2 (a.k.a. ACO1 and IREB2, respectively) (Kühn, 2015). IRPs respond to changes in cellular iron levels and in turn enact posttranscriptional regulation of key iron metabolism genes via their interaction with cis-regulatory iron responsive elements (IREs) present on target mRNAs, including those encoding the transferrin receptor (TFR1), the ferritin-H (FTH1) and ferritin-L (FTL1) iron storage proteins, and the iron exporter FPN. The role of macrophage IRPs in body iron recycling and immunity is not known.

Here we use Cre/Lox technology to generate mice with cell-type selective, complete loss of IRP expression in macrophages. Earlier work investigating mice with complete IRP deficiency in hepatocytes or duodenal enterocytes, respectively, had shown early postnatal death in both cases, reflecting essential functions of the IRPs for organismal survival (Galy et al., 2008, 2010). This study reveals important molecular functions of the IRPs in the control of macrophage iron metabolism and uncovers that at least this mammalian cell type is viable without IRPs; it also unveils the critical importance of the IRP/IRE system for macrophage-mediated immunity and host resistance to infection with intracellular bacteria.

RESULTS

Role of IRPs in Macrophage and Body Iron Homeostasis

Animals homozygous for floxed *Irp* alleles (*Aco1*$^{flox/flox}$, *Ireb2*$^{flox/flox}$) (Galy et al., 2005) were bred to a mouse line with targeted insertion of *Cre* into the *Lysozyme2* (*Lyz2*) locus enabling selective expression of CRE recombinase in monocytes/macrophages and neutrophils (Clausen et al., 1999). *Aco1*$^{flox/flox}$,*Ireb2*$^{flox/flox}$,*Lyz2*$^{+/Cre}$ mice (designated *Irp*$^{LyzCre(+)}$)