Iron ERRs with *Salmonella*

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http://dx.doi.org/10.1016/j.chom.2014.04.012

The hormone hepcidin promotes iron sequestration by macrophages. A recent study by Kim et al. (2014) implicates the orphan receptor ERRγ (estrogen-related receptor γ) in the regulation of hepcidin production and suggests that targeting the ERRγ-hepcidin axis may be beneficial during infection with the facultative intracellular pathogen *Salmonella*.

Macrophages play a central role in scavenging and recycling iron from senescent red blood cells. This process is controlled by the master regulatory hormone hepcidin, which is primarily synthesized in the liver. During inflammation, the interleukin-6 (IL-6)-inducible peptide hepcidin promotes the degradation of its receptor, the iron exporter ferroportin, resulting in iron retention by macrophages, reduced intestinal iron absorption, and hypoferremia. While this iron-withholding response is a central component of innate nutritional immunity that restricts iron availability to circulating microbes (Weiss and Schett, 2013; Cassat and Skaar, 2013), intracellular bacteria such as *Salmonella* have been shown to benefit from the iron retained within macrophages.

Adding to our understanding of iron regulation during infection, a new study by Kim et al. (2014) has implicated ERRγ (estrogen-related receptor γ, also called NR3B3), a nuclear hormone receptor with no known activating ligand, in the control of iron withholding. In this study, *Salmonella enterica* sv. Typhimurium was shown to induce hepcidin expression, hypoferremia, and ERRγ expression in mice. IL-6 knockout (KO) mice failed to exhibit these responses and were observed to have lower bacterial burdens, indicating that ERRγ acts downstream of IL-6 and has a detrimental effect on host defense against *Salmonella*. ERRγ expression was shown to result from transactivation by the transcription factor STAT3. The researchers further showed that overexpression of ERRγ induces hepcidin production and hypoferremia, and they were able to identify an ERRγ response element in the hepcidin promoter. ERRγ did not affect expression of NOS2 (inducible nitric oxide synthase), which can also alter iron trafficking in macrophages by stimulating iron export via ferroportin (Nairz et al., 2013). A reverse agonist designated GSK5182, which binds the ERRγ receptor and decreases its activity, was able to ameliorate *Salmonella*-induced hepcidin expression, hypoferremia, and iron accumulation in the liver and spleen, along with a reduction in bacterial burden, macrophage iron content, and proinflammatory cytokine production. The authors attributed the detrimental effects of hepcidin to increased iron availability in the macrophages where *Salmonella* resides (Figure 1). They suggested that ERRγ and hepcidin might be therapeutically targeted to treat infections with intracellular pathogens.

This study represents a significant advance in our understanding of the regulatory linkage between innate immune responses and iron homeostasis. Previous work by the same group has shown that ERRγ controls hepatic glucose production in response to glucagon (Kim et al., 2012), and it will be interesting to see whether ERRγ can account for the observed association between IL-6 and hyperglycemia in septic patients.

In considering the pharmacological targeting of this pathway to treat infection with intracellular pathogens, a few caveats are in order. First, observations regarding the effects of hepcidin during *Salmonella* infection have been somewhat conflicting. Kim et al. (2014) found that antagonism of hepcidin by the inhibition of ERRγ signaling is beneficial during systemic *Salmonella* infection. This is consistent with earlier observations showing that hepcidin antagonism can ameliorate *Salmonella*-induced inflammation (Wang et al., 2009) and that HFE mice, which have deficient hepcidin expression, are able to restrict *Salmonella* replication (Nairz et al., 2009). However, in contrast, hepcidin-deficient mice on a different genetic background are reportedly more susceptible to *Salmonella* challenge, and hepcidin administration can enhance the survival these mice during *Salmonella* infection (Yuki et al., 2013). Differences in inoculum size, mouse strain, route of infection, iron distribution in tissues, and effects of partial versus complete ERRγ/hepcidin inhibition are among the variables that should be further explored to explain these discrepant findings.

Second, in addition to its regulation of ferroportin, hepcidin can modulate host inflammatory responses (Pagani et al., 2011). Intracellular iron levels per se are immunomodulatory, and the disruption of iron homeostasis affects proinflammatory cytokine production, either directly via regulation of interferon gamma (IFN-γ) activity or by modulating the production of nitric oxide or reactive oxygen species, which in turn affect redox-sensitive signaling pathways (Nairz et al., 2013; Pagani et al., 2011; Weiss and Schett, 2013). In view of the relatively modest effects of GSK5182 on bacterial burden, particularly in the spleen, it is conceivable that the survival benefit observed by Kim et al. (2014) following GSK5182 treatment might be attributable in part to reduced immunopathology rather than to antimicrobial effects resulting from lessened iron availability. Previous studies have suggested that hepcidin antagonists can ameliorate inflammation in *Salmonella* enterocolitis (Wang et al., 2009), and effects of iron homeostasis on T lymphocyte and macrophage polarization

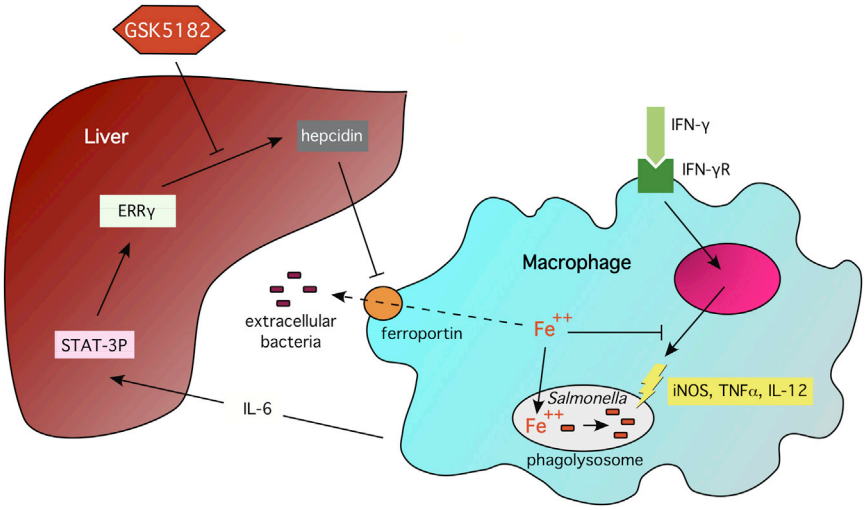

Figure 1. Estrogen-Related Receptor γ Regulates Host Iron Trafficking by Inducing Hepcidin Formation in the Liver

ERRγ transcription is stimulated by interleukin-6 (IL-6) and the transcription factor STAT3. Hepcidin is released into the circulation and binds to the iron export protein ferroportin 1 (FP1), resulting in FP1 degradation and macrophage iron retention. This results in systemic hypoferremia but increases access of the intracellular pathogen *Salmonella* to iron. The increase in macrophage iron levels also inhibits interferon-γ-dependent antibacterial immune responses. ERRγ inhibition by the reverse agonist GSK5182 counteracts the effects of hepcidin on intramacrophage iron availability and antimicrobial immune effector pathways but may increase the availability of iron to extracellular pathogens.

have been described (Weiss and Schett, 2013). Immunomodulatory actions of ERRγ and hepcidin will have to be carefully considered when targeting these proteins during infection, as such actions may be either protective or detrimental depending on the nature and primary localization of the microbe and time course of the specific host-pathogen interaction (Cassat and Skaar, 2013; Drakesmith and Prentice, 2012).

Finally, it must be remembered that the changes in iron compartmentalization mediated by hepcidin can restrict the growth of pathogens at some tissue sites and in the circulation while having the opposite effect on intracellular pathogens. Accordingly, hepcidin plays a protective antimicrobial role in host resistance to *Vibrio vulnificus*, *Yersinia*, and *Plasmodium* spp., despite promoting the growth of *Salmonella*, *Leishmania*, and mycobacteria in macrophages (Cassat and Skaar, 2013; Drakesmith and Prentice, 2012; Nairz et al., 2013). Therapeutic targeting of the ERRγ-hepcidin-ferroportin axis during infection will therefore require a detailed knowledge of the cellular localization of the specific pathogen involved. Coinfection with malaria and *Salmonella* or tuberculosis, not an infrequent scenario in Africa, would pose a therapeutic dilemma from an iron standpoint. Depriving one pathogen only to benefit another would be, one might say, ironic.

ACKNOWLEDGMENTS

F.C.F. is supported by NIH grants AI39557, AI55396, and AI101084. G.W. is supported by a grant from the Austrian Research Fund (TRP-188).

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