Congratulations to Drs Xiao, Christian and Babitt, members of the Utah Center for Iron and Heme Disorders, for their recent publication “BMP5 contributes to hepcidin regulation and systemic iron homeostasis in mice”. For details see the full article

Abstract

Hepcidin is the master regulator of systemic iron homeostasis. The bone morphogenetic protein (BMP) signaling pathway is a critical regulator of hepcidin expression in response to iron and erythropoietic drive. Although endothelial-derived BMP6 and BMP2 ligands have key functional roles as endogenous hepcidin regulators, both iron and erythropoietic drives still regulate hepcidin in mice lacking either or both ligands. Here, we used mice with an inactivating *Bmp5* mutation (*Bmp5*^{se}), either alone or together with a global or endothelial *Bmp6* knockout, to investigate the functional role of BMP5 in hepcidin and systemic iron homeostasis regulation. We showed that *Bmp5*^{se}-mutant mice exhibit hepcidin deficiency at age 10 days, blunted hepcidin induction in response to oral iron gavage, and mild liver iron loading when fed on a low- or high-iron diet. Loss of 1 or 2 functional *Bmp5* alleles also leads to increased iron loading in *Bmp6*-heterozygous mice and more profound hemochromatosis in global or endothelial *Bmp6*-knockout mice. Moreover, double *Bmp5*- and *Bmp6*-mutant mice fail to induce hepcidin in response to long-term dietary iron loading. Finally, erythroferrone binds directly to BMP5 and inhibits BMP5 induction of hepcidin in vitro. Although erythropoietin suppresses hepcidin in *Bmp5*^{se}-mutant mice, it fails to suppress hepcidin in double *Bmp5*- and *Bmp6*-mutant males. Together, these data demonstrate that BMP5 plays a functional role in hepcidin and iron homeostasis regulation, particularly under conditions in which BMP6 is limited.